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17

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÷ single-dose prophylaxis/ twice-daily treatment

P, 24,809

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In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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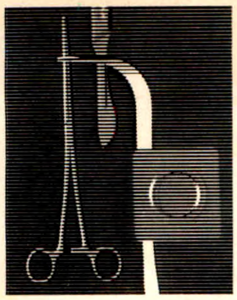

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INDICATIONS AND USAGE

Treatment: CEFOTAN is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary Tract Infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis,* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).
Lower Respiratory Tract Infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), *E coli, Proteus mirabilis,* and *Serratia marcescens.**
Skin and Skin Structure Infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus* species (excluding enterococci), *E coli, Klebsiella pneumoniae,* and *Peptococcus** and *Peptostreptococcus* sp.*
Gynecologic Infections caused by *Staphylococcus aureus* (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), group B streptococci, *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, and B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species).
Intra-abdominal Infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Streptococcus* species (excluding enterococci), *Bacteroides* species (excluding *B distasonis, B ovatus,* and *B thetaiotaomicron*), and *Clostridium* species.*
Bone and Joint Infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

Note: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

Prophylaxis: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity and, possibly, subsequent bleeding. Those at increased risk include patients with renal or hepatobiliary impairment or poor nutritional state, the elderly, and patients with cancer. Prothrombin time should be monitored and exogenous vitamin K administered as indicated.

PRECAUTIONS

General: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Information for Patients: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

Drug Interactions: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

Drug/Laboratory Test Interactions: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

Usage in Pregnancy: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Usage in Nursing Mothers: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

During postmarketing experience with CEFOTAN, agranulocytosis, anaphylactic reactions, fever, hemolytic anemia, leukopenia, prolonged prothrombin time with or without bleeding, pseudomembranous colitis, and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION

Treatment: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

Prophylaxis: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

Impaired Renal Function: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:}\quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:}\quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

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Judah Folkman, M.D.
Boston, Massachusetts

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San Francisco, California

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Jeffrey A. Norton, M.D., John L. Doppman, M.D., and Robert T. Jensen, M.D.
Bethesda, Maryland

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Kazutomo Inoue, M.D., Akira Fuchigami, M.D., Shunichi Higashide, M.D., Shoichiro Sumi, M.D., Masafumi Kogire, M.D., Takashi Suzuki, M.D., and Takayoshi Tobe, M.D., F.A.C.S.
Kyoto and Yamaguchi, Japan

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Naomi Iwai, Jun Yanagihara, Kazuaki Tokiwa, Takashi Shimotake, and Kaori Nakamura
Kyoto, Japan

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Henri Bismuth, M.D., F.A.C.S.(HON.), Richard Nakache, M.D., and Tom Diamond, M.D., F.R.C.S.
Villejuif, France

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Rochester, Minnesota

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Boston, Massachusetts

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Eric W. Fonkalsrud, M.D., and Nancy Loar, R.N.
Los Angeles, California

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Gordon H. Hafner, M.D., Lemuel Herrera, M.D., F.A.C.S., and Nicholas J. Petrelli, M.D., F.A.C.S.
Buffalo, New York

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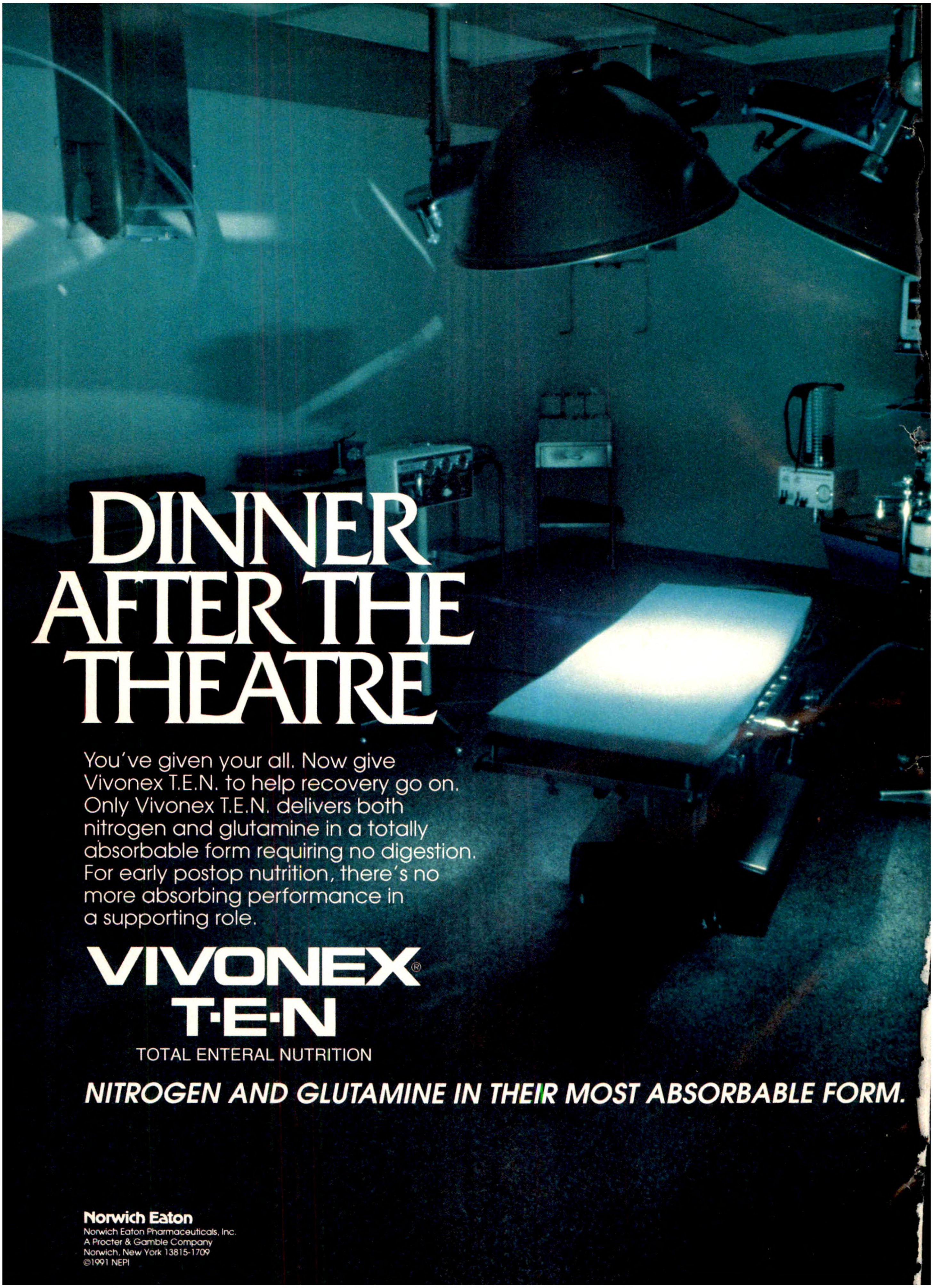
Eng-Hen Ng, M.D., Raphael E. Pollock, M.D., PH.D., Mark F. Munsell, M.S., Edward N. Atkinson, PH.D., and Marvin M. Romsdahl, M.D., PH.D.
Houston, Texas



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Nashville, Tennessee

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James G. Geraghty, M.CH., F.R.C.S.I., Eamonn C. Coveney, M.B., Michael Kiernan, and
Niall J. O'Higgins, M.D., F.R.C.S.I.
Dublin, Ireland

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Lawrence W. Way, M.D.
San Francisco, California

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Andrew M. Davidoff, M.D., Theodore N. Pappas, M.D., Elizabeth A. Murray, R.N., David J. Hilleren, M.D., Randall D. Johnson, M.D., Mark E. Baker, M.D., Glenn E. Newman, M.D., Peter B. Cotton, M.D., and William C. Meyers, M.D.
Durham and Asheville, North Carolina

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A. R. Moossa, M.D., David W. Easter, M.D., Eric Van Sonnenberg, M.D., Giovanna Casola, M.D., and Horacio D'Agostino, M.D.
San Diego, California

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John L. Flowers, M.D., Karl A. Zucker, M.D., Scott M. Graham, M.D., William A. Scovill, M.D., Anthony L. Imbembo, M.D., and Robert W. Bailey, M.D.
Baltimore, Maryland

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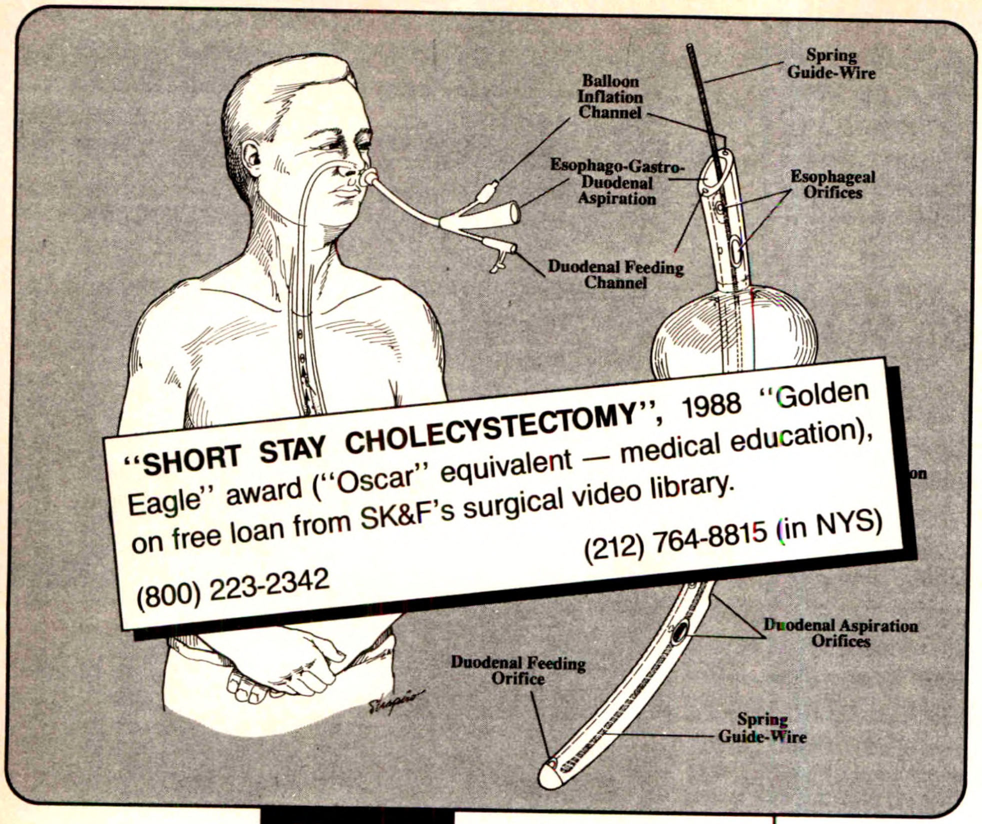

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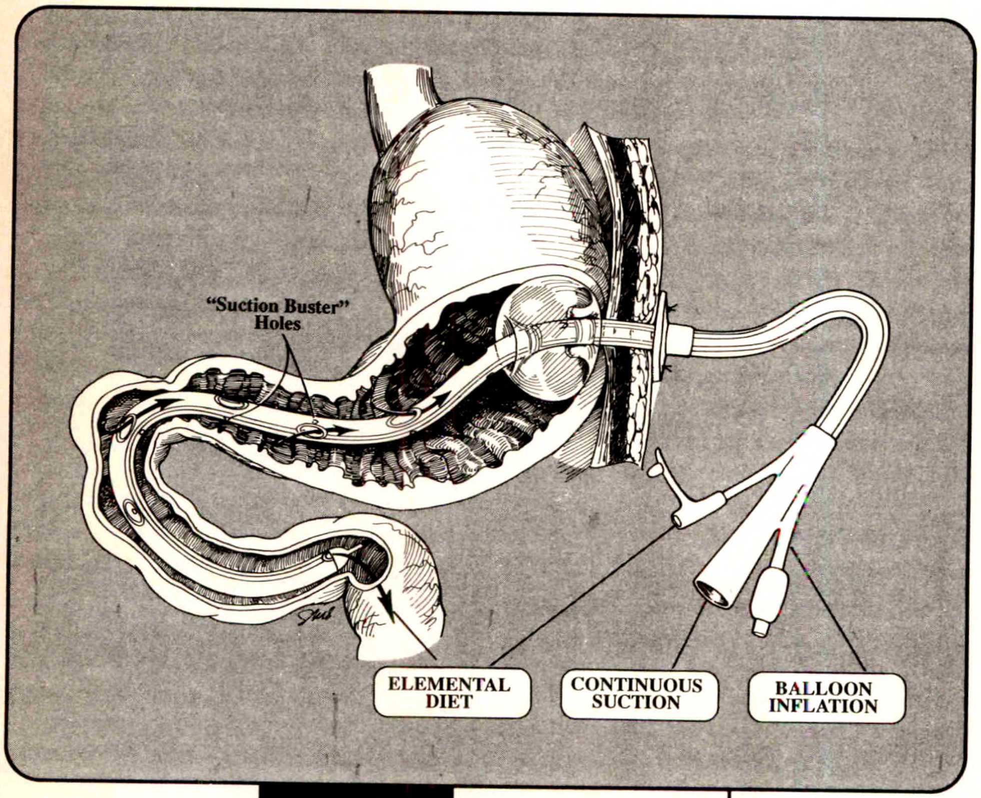

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functional survival. Significant risk factors included immunosuppressive protocol, recipient category, retransplantation, donor hyperglycemia, and poor HLA matching.

Paul F. Gores, M.D., *Kristen J. Gillingham,* M.S., *David L. Dunn,* M.D., PH.D.,
Kay C. Moudry-Munns, R.N.C., C.C.R.N., *John S. Najarian,* M.D., *and David E. R. Sutherland,* M.D., PH.D.
Minneapolis, Minnesota

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Osamu Ishikawa, M.D., *Hiroaki Ohigashi,* M.D., *Shingi Imaoka,* M.D., *Hiroshi Furukawa,* M.D.,
Yo Sasaki, M.D., *Makoto Fujita,* M.D., *Chikazumi Kuroda,* M.D., *and Takeshi Iwanaga,* M.D.
Osaka, Japan

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Lyon, France

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Charles N. Mock, M.D., *Joseph Amaral,* M.D., *and Lucia E. Visser,* M.D.
Providence, Rhode Island, and Berekum, Ghana

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Arve Saebø, M.D., *and Jørgen Lassen,* M.D.
Bergen and Oslo, Norway

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Wim Timens, M.D., *and Rob Leemans,* M.D.
Groningen and Leeuwarden, The Netherlands

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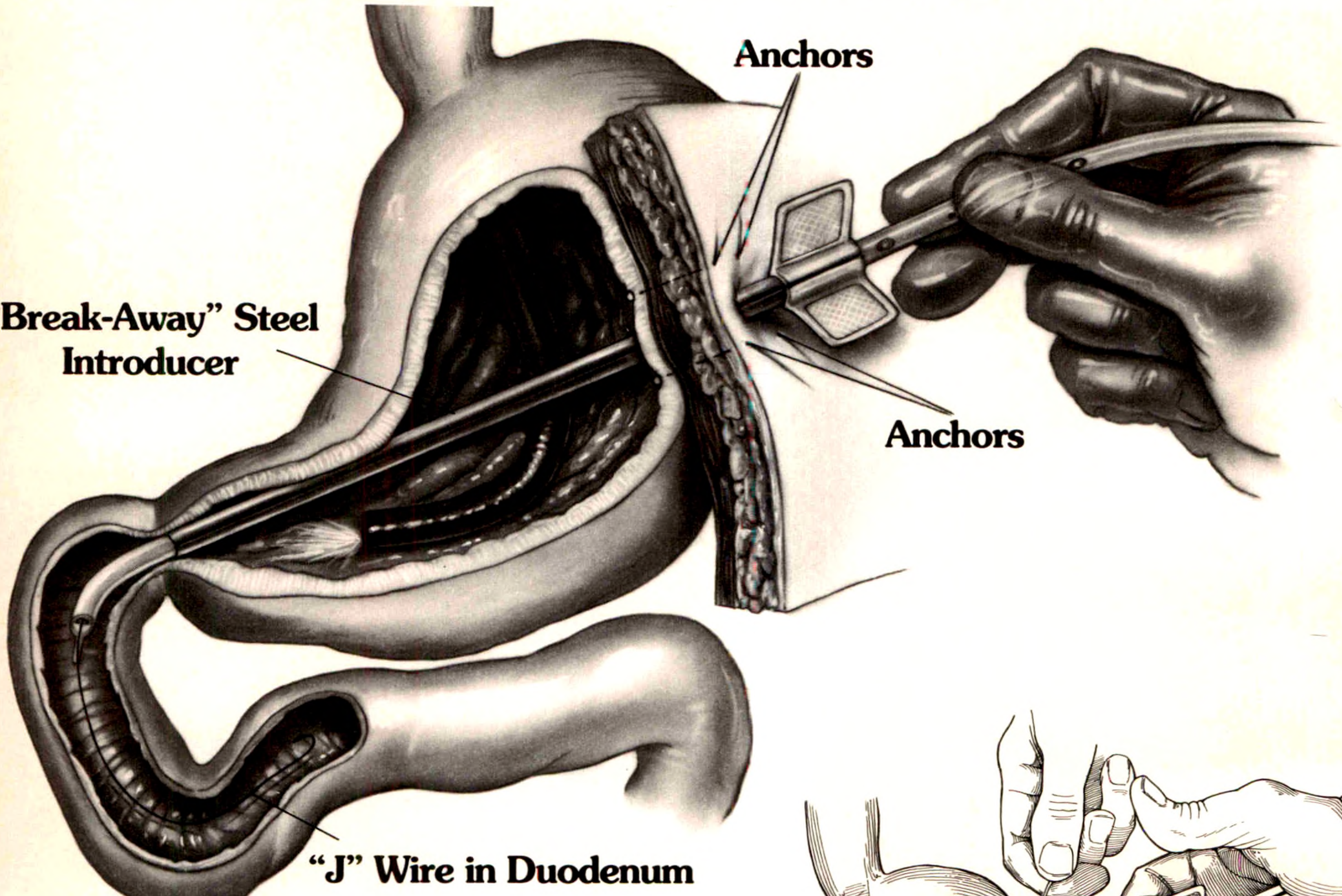

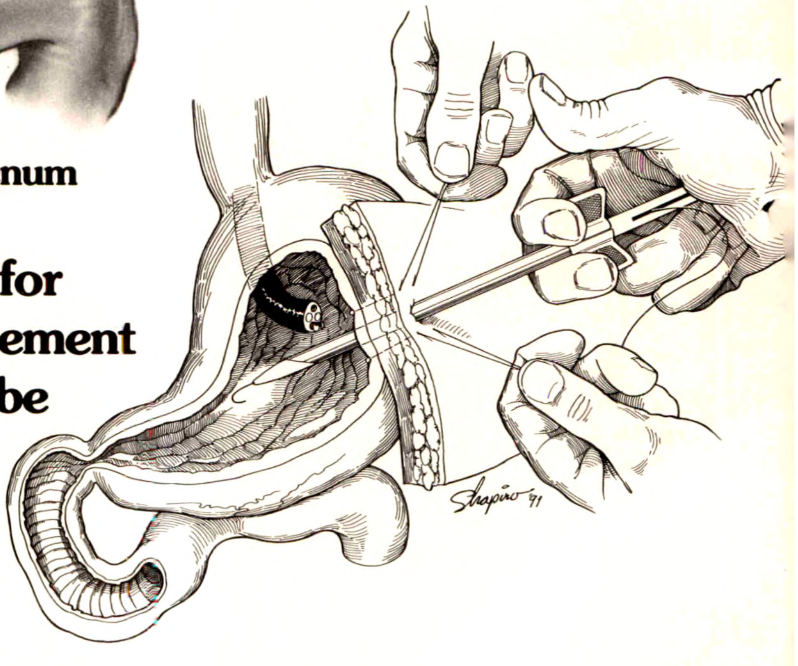

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six patients received no homologous transfusions. Hilar lacerations were repaired by temporarily cross-clamping the splenic pedicle and oversewing torn polar vessels via the injury defect. This approach minimizes the risk of both homologous transfusion and asplenia.

Charles L. Witte, M.D., Michael J. Esser, M.D., and William D. Rappaport, M.D.
Tucson, Arizona

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G. C. Zografos, K. Martis, and D. L. Morris
Nottingham, England

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William C. Williard, M.D., Steven I. Hajdu, M.D., Ephraim S. Casper, M.D., and Murray F. Brennan, M.D.
New York, New York

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Tamer Tadros, M.D., Theo Wobbes, M.D., PH.D., and Thijs Hendriks, PH.D.
Nijmegen, The Netherlands

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Jonathan B. Koea, M.H.B., M.B., CH.B., and James H. F. Shaw, M.D., F.R.A.C.S.
Auckland, New Zealand

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Robert A. Edmondson, F.R.C.S., Anjan K. Banerjee, M.R.C.P., F.R.C.S., and John A. Rennie, M.S., F.R.C.S.
London, England

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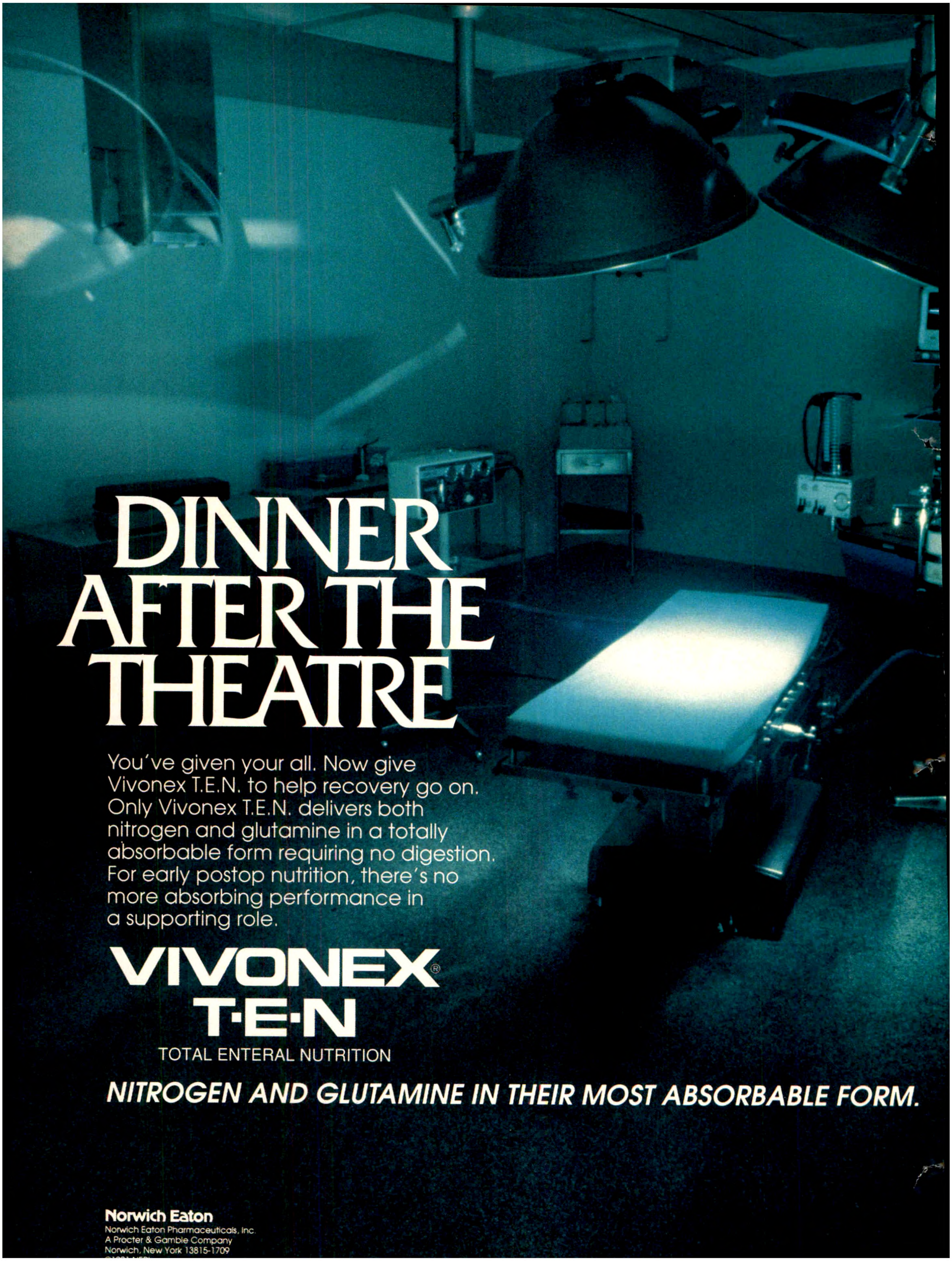

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Jeffrey A. Norton, M.D.
Bethesda, Maryland

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Primary Hyperparathyroidism in the 1990s: Choice of Surgical Procedures for This Disease 300

In recent years many advances have been made in the diagnosis and treatment of primary hyperparathyroidism. The theoretical advantages and disadvantages of a unilateral *versus* a bilateral neck exploration for this condition are discussed. The authors urge the routine use of bilateral neck exploration in the initial surgery for primary hyperparathyroidism and give reasons for this choice.

Edwin L. Kaplan, M.D., *Tohru Yashiro,* M.D., *and George Salti,* B.A.
Chicago, Illinois

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Cholecystectomy: The Impact of Socioeconomic Change 318

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Kimberly D. Saunders-Kirkwood, M.D., *Bernardo Aizen,* M.D., *Jesse E. Thompson, Jr.,* M.D.,
Michael J. Zinner, M.D., *Joe A. Cates,* M.D., *Robert Bennion,* M.D., *John Gill,* M.D., *Frarzin Boudi,* B.A.,
and Joel J. Roslyn, M.D.
Los Angeles, California

Inapparent Carcinoma of the Gallbladder: An Appraisal of a Radical Second Operation After Simple Cholecystectomy 326

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Yoshio Shirai, M.D., *Keisuke Yoshida,* M.D., *Kazuhiro Tsukada,* M.D., *and Terukazu Muto,* M.D.
Niigata, Japan

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Louis F. Martin, M.D., Frank V. McL. Booth, M.D., H. David Reines, M.D., Lawrence G. Deysach, M.A., Ronald L. Kochman, M.S., Lorri J. Erhardt, B.S., M.T., and G. Steven Geis, PH.D., M.D.
Hershey, Pennsylvania; Buffalo, New York; Richmond, Virginia; Skokie, Illinois

Reduction in Biliary IgA After Burn Injury: Role of Diminished Delivery via the Thoracic Duct and of Enhanced Loss From the Systemic Circulation 338

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W. A. Cappeller, K. J. Bloch, R. A. Hatz, E. A. Carter, J. Fagundes, D. A. Sullivan, and P. R. Harmatz
Boston, Massachusetts; Münich, Germany

Clinicopathologic Studies on Perineural Invasion of Bile Duct Carcinoma 344

The spread of bile duct carcinoma through the perineural space and its clinicopathologic significance were studied in 70 patients who underwent resection for bile duct cancer. The overall incidence of perineural invasion in the resected specimen was 81.4%. A group of patients who did not have perineural invasion showed better postoperative survival than a group of patients who had perineural invasion.

Md. Mukhlesur Rahman Bhuiya, M.B.B.S., Yuji Nimura, M.D., Junichi Kamiya, M.D., Satoshi Kondo, M.D., Shinji Fukata, M.D., Naokazu Hayakawa, M.D., and Shigehiko Shionoya, M.D.
Nagoya, Japan

Prognostic Value of Serum CA 19-9 Levels in Pancreatic Adenocarcinoma 350

Relatively proportional to the tumor burden, measurement of the serum CA 19-9 titer before operation in patients with cancer of the exocrine pancreas is proving to be a useful adjunct to management. Elevated before resection in 85% to 90% of patients, a fall to the normal range after resection connotes a relatively good prognosis. Once the level has fallen after resection, a subsequent elevation in the CA 19-9 titer may be the first indication of recurrent disease.

Fuzhou Tian, M.D., Hubert E. Appert, PH.D., Jonathan Myles, M.D., and John M. Howard, M.D.
Toledo, Ohio

Cytokine Serum Level During Severe Sepsis in Human IL-6 as a Marker of Severity 356

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Pierre Damas, M.D., Didier Ledoux, M.D., Monique Nys, Yvonne Vrindts, Donat De Groote, M.D., Paul Franchimont, M.D., and Maurice Lamy, M.D.
Liège, Belgium

Delayed Gastric Emptying After Roux-en-Y due to Four Types of Partial Obstruction 363

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George F. Gowen, M.D.
Philadelphia, Pennsylvania

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Rolf Loertscher, M.D., *Ludger Blier,* M.D., *Oren Steinmetz,* M.D., *and Carl Nohr,* M.D., PH.D.
Montreal, Quebec, Canada

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Gurdev Singh, F.R.C.S., *Khalil I. Chaudry, and Irshad H. Chaudry,* PH.D.
East Lansing, Michigan

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John Christiansen, M.D., *and Bo Sparsø,* M.D.
Copenhagen, Denmark

ADVANCES IN SURGICAL TECHNIQUE

Long-limb Gastric Bypass in the Superobese: A Prospective Randomized Study **387**

A modification of RY gastric bypass in which bile and pancreatic secretions were diverted more distally in the gastrointestinal tract was prospectively compared with conventional RYGB over a 7-year period. The distal modification resulted in significantly greater weight loss at 2 and 3 years postoperatively. There was no difference in complication rate between the two procedures.

Robert E. Brolin, M.D., F.A.C.S., *Hallis A. Kenler,* PH.D., R.D., *Joseph H. Gorman,* B.S., *and Ronald P. Cody,* PH.D.
New Brunswick, New Jersey

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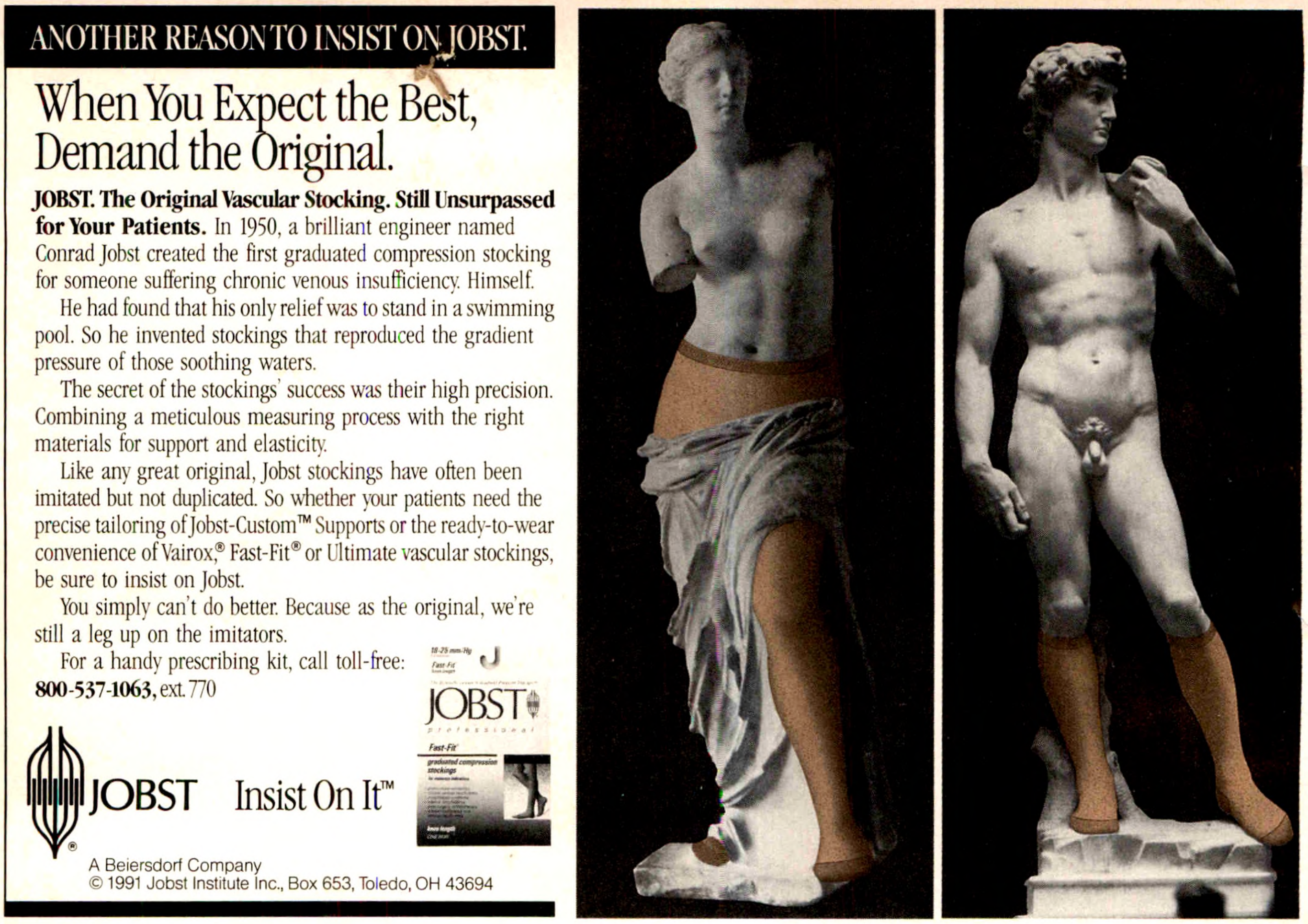

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John Ochsner, M.D.
New Orleans, Louisiana

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Denton A. Cooley, M.D., O. H. Frazier, M.D., J. Michael Duncan, M.D., George J. Reul, M.D., and Zvonimir Krajcer, M.D.
Houston, Texas

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Joseph M. Craver, M.D., William S. Weintraub, M.D., Ellis L. Jones, M.D., Robert A. Guyton, M.D., and Charles R. Hatcher, Jr., M.D.
Atlanta, Georgia

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Mario N. Gomes, M.D., Peter L. Choyke, M.D., and Robert B. Wallace, M.D.
Washington, DC, and Bethesda, Maryland

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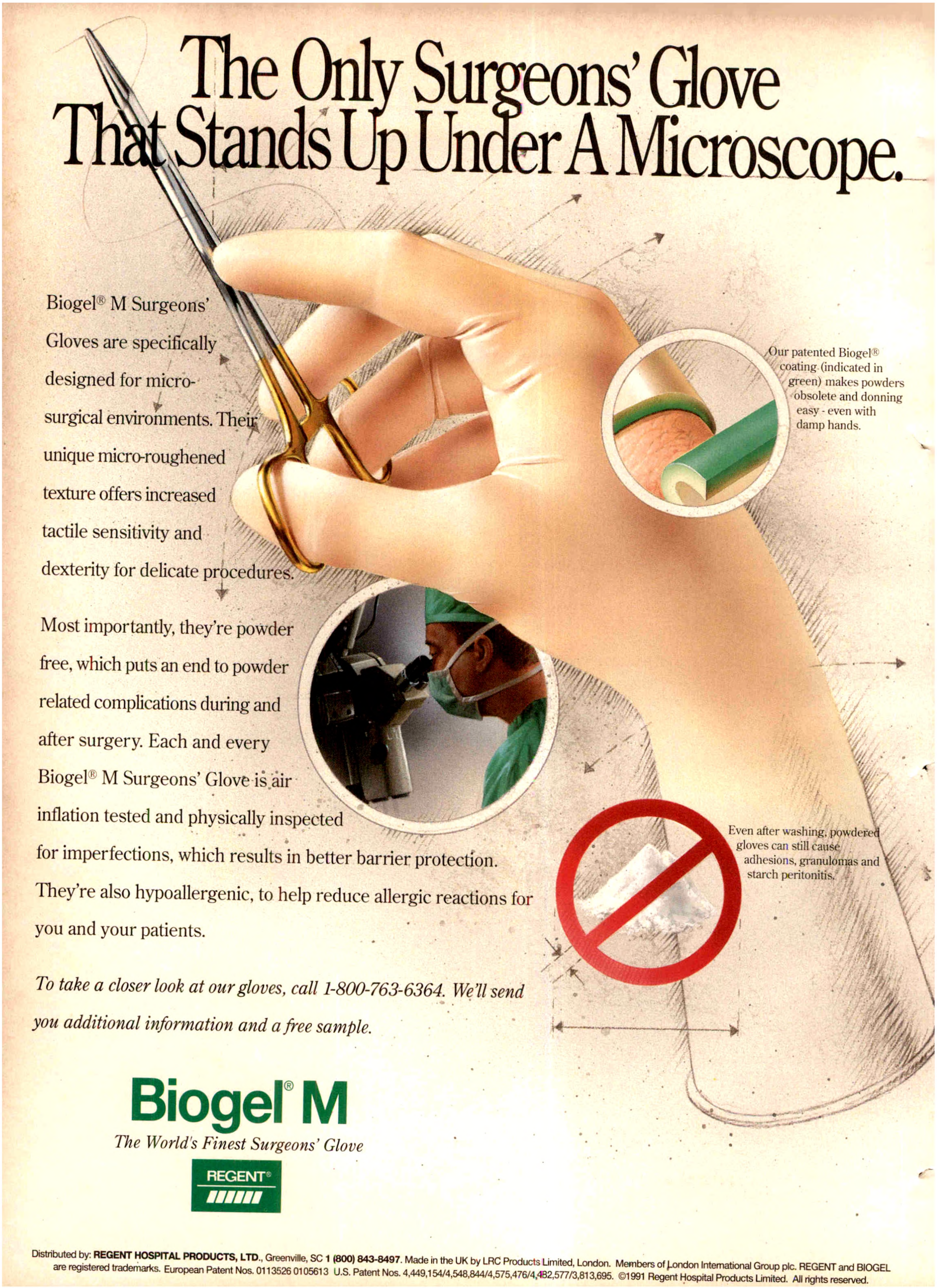

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Juxtarenal Aortic Occlusion **443**

The authors review 113 aortic occlusions in 103 patients seen during a 26-year period (1965–1991). They found three distinct patterns of presentation that ultimately affected management, operative mortality, and long-term outcome. The evolution of current treatment strategies is reviewed.

S. Scott Tapper, M.D., Judith M. Jenkins, R.N., M.S.N., William H. Edwards, M.D.,
Joseph L. Mulherin, Jr., M.D., Raymond S. Martin, III, and William H. Edwards, Jr., M.D.
Nashville, Tennessee

Current Management of Male Breast Cancer: A Review of 104 Cases **451**

The authors report a retrospective review of 104 male patients with breast cancer. The results suggest that the disease is remarkably similar to breast cancer in female patients, with virtually identical survival profiles. The poor prognosis of men reported in earlier series may be yielding to increased public awareness of the disease and, specifically, an awareness of the value of prompt diagnosis and treatment.

Patrick I. Borgen, M.D., George Y. Wong, PH.D., Vaia Vlamis, M.S., Charles Potter, Brian Hoffmann, M.D.,
David W. Kinne, M.D., Michael P. Osborne, M.D., and William M. P. McKinnon, M.D.
New York, New York, and New Orleans, Louisiana

Total IgE in Plasma is Elevated After Traumatic Injury and is Associated With Sepsis Syndrome **460**

The authors report that total plasma IgE levels from 32 patients with major traumatic injury were elevated compared with levels in control groups of healthy volunteers and patients undergoing elective surgery. Also, in the trauma group, total IgE levels were elevated in patients with sepsis syndrome.

Joseph T. DiPiro, PHARM.D., Robert G. Hamilton, PH.D., Thomas R. Howdieshell, M.D.,
N. Franklin Adkinson, Jr., M.D., and Arlie R. Mansberger, Jr., M.D.
Athens and Augusta, Georgia, and Baltimore, Maryland

Abdominal Packing for Surgically Uncontrollable Hemorrhage **467**

Abdominal packing for hemorrhage that is not controlled by standard techniques in patients who have had hypothermic, acidotic, and coagulopathic trauma may be lifesaving. Factors that adversely affect survival were identified as pH $\leqslant 7.18$, T $\leqslant$ 33C, prothrombin time $\geqslant$16 seconds, partial thromboplastin time $\geqslant$50, and transfusion of $\geqslant$10 units of blood. Packing may aid aggressive attempts to prevent or correct these factors.

Kenneth W. Sharp, M.D., and Richard J. Locicero, M.D.
Nashville, Tennessee

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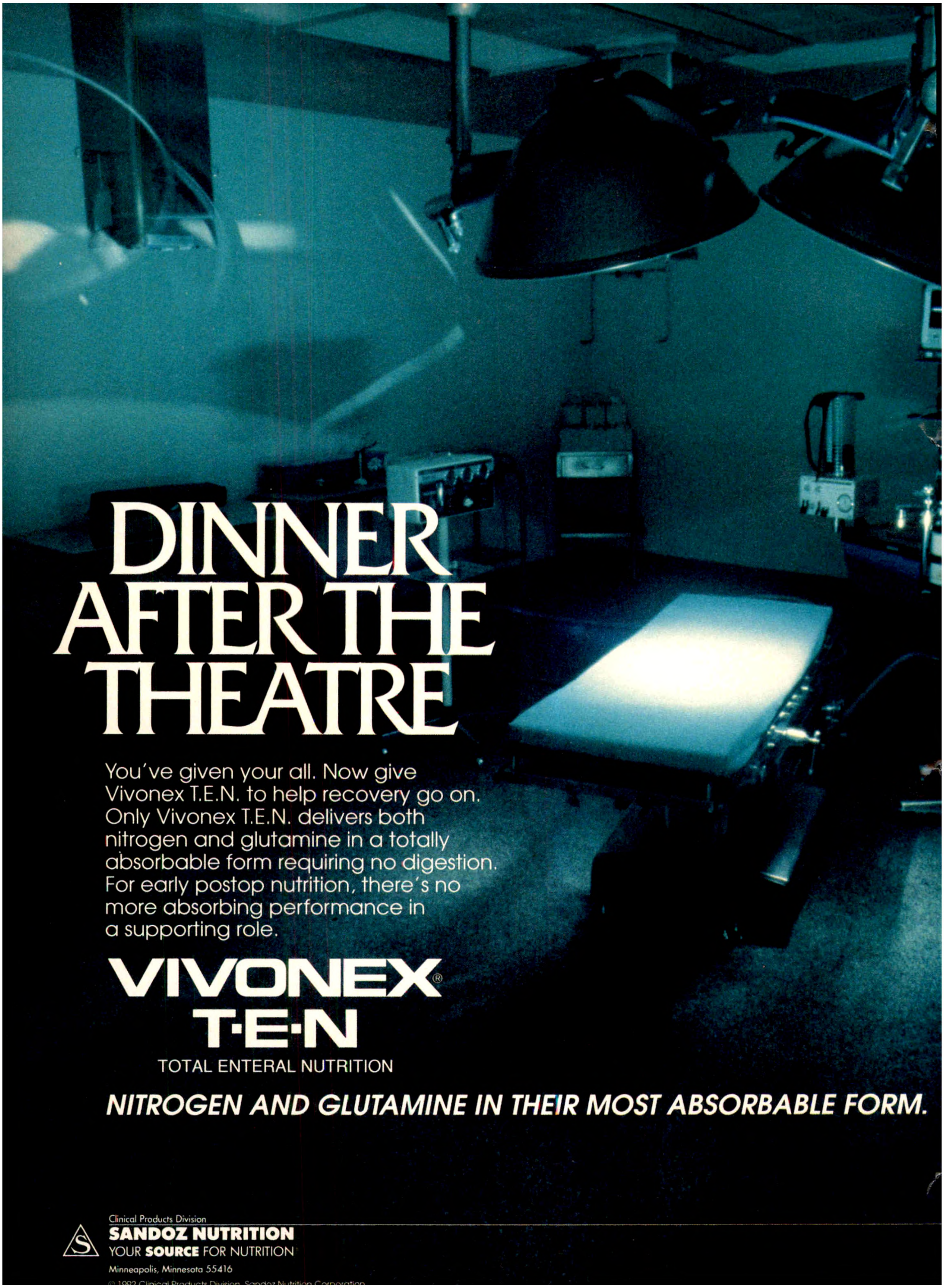
Jon M. Burch, M.D., Victor B. Ortiz, B.A., Robert J. Richardson, M.D., R. Russell Martin, M.D.,
Kenneth L. Mattox, M.D., and George L. Jordan, Jr., M.D.
Houston, Texas, and the Tripler Army Medical Center, Hawaii

Control of the Hypermetabolic Response to Burn Injury Using Environmental Factors **485**

The hypermetabolic response to burn injury can be greatly reduced with occlusive dressings (insulation) or electromagnetic heaters and no dressings (external energy support). The residual hypermetabolic response may be secondary to chronic increase in body temperature. Catecholamines are not the primary mediators of the hypermetabolic response.

Fred T. Caldwell, Jr., M.D., Bonny H. Wallace, M.H.S.A., John B. Cone, M.D., and Linda Manuel
Little Rock, Arkansas



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H. Leon Pachter, M.D.*, Frank C. Spencer,* M.D.*, Steven R. Hofstetter,* M.D.*, Howard G. Liang,* M.D.*,*
and Gene F. Coppa, M.D.
New York, New York

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Kenneth A. Kudsk, M.D.*, Martin A. Croce,* M.D.*, Timothy C. Fabian,* M.D.*, Gayle Minard,* M.D.*,*
Elizabeth A. Tolley, PH.D.*, H. Andrew Poret,* M.D.*, Melody R. Kuhl,* R.N.*, and Rex O. Brown,* PHARM.D.
Memphis, Tennessee

Carotid Endarterectomy Monitored With Transcranial Doppler **514**

The authors report intraoperative transcranial Doppler monitoring of cerebral ischemia during carotid clamping in 238 carotid artery operations. If intracranial Doppler velocity showed severe ischemia, carotid shunting was associated with a lower stroke rate, but not in patients who had mild ischemia or no ischemia. Electroencephalogram and carotid stump pressure were not as helpful.

Holt A. McDowell, Jr., M.D.*, Gary M. Gross,* M.D.*, and James H. Halsey,* M.D.
Birmingham, Alabama

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Masaski Izukura, M.D.*, B. Mark Evers,* M.D.*, Dilipkumar Parekh,* M.D.*, Keigo Yoshinaga,* M.D.*,*
Tatsuo Uchida, M.S.*, Courtney M. Townsend, Jr.,* M.D.*, and James C. Thompson,* M.D.
Osaka and Tokyo, Japan, Johannesburg, South Africa, and Galveston, Texas

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Jin Ishizuka, M.D.*, Jean Martinez,* PH.D.*, Courtney M. Townsend, Jr.,* M.D.*, and James C. Thompson,* M.D.
Galveston, Texas, and Montpellier, France

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Wiley W. Souba, M.D.*,* SC.D.*, and Edward M. Copeland,* M.D.
Gainesville, Florida

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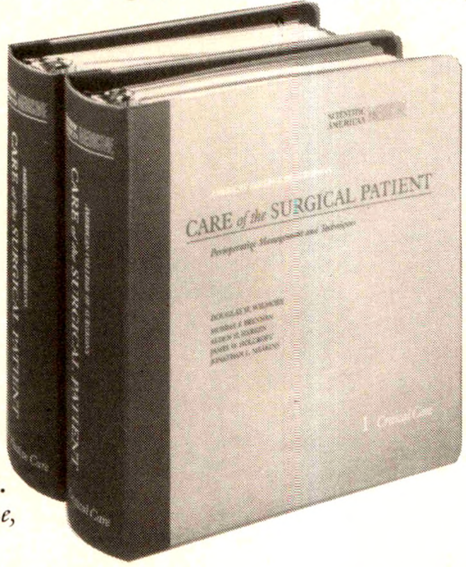

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John L. Cameron, M.D., Stanley R. Hamilton, M.D., Joann Coleman, R.N., James V. Sitzmann, M.D., and Theodore M. Bayless, M.D.
Baltimore, Maryland

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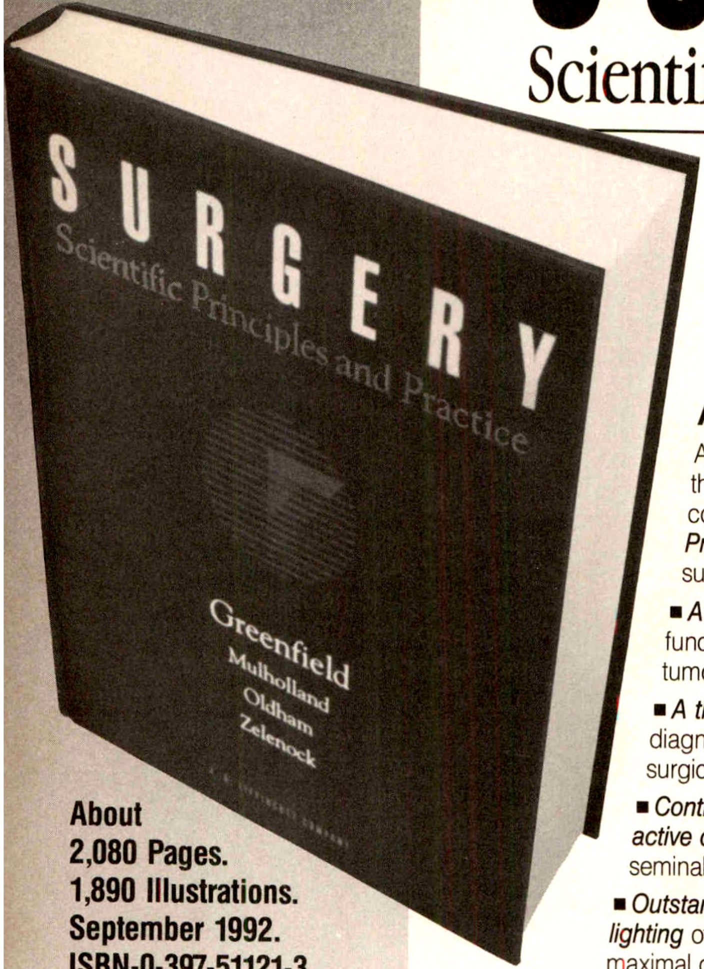

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John A. Goss, M.D.*, Martin J. Mangino,* PH.D.*, and M. Wayne Flye,* M.D., PH.D.
St. Louis, Missouri

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David R. Farley, M.D.*, Jon A. van Heerden,* M.B., CH.B., F.A.C.S., F.R.C.S.(Edin)(Hon),
Clive S. Grant, M.D., F.A.C.S.*, Laurence J. Miller,* M.D.*, and Duane M. Ilstrup,* M.S.
Rochester, Minnesota

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David B. Adams, M.D.*, and Marion C. Anderson,* M.D.
Charleston, South Carolina

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Folkert O. Belzer, M.D.*, Anthony M. D'Alessandro,* M.D.*, Robert M. Hoffmann, Stuart J. Knechtle,* M.D.,
Alan Reed, M.D.*, John D. Pirsch,* M.D.*, Munci Kalayoglu,* M.D.*, and Hans W. Sollinger,* M.D., PH.D.
Madison, Wisconsin

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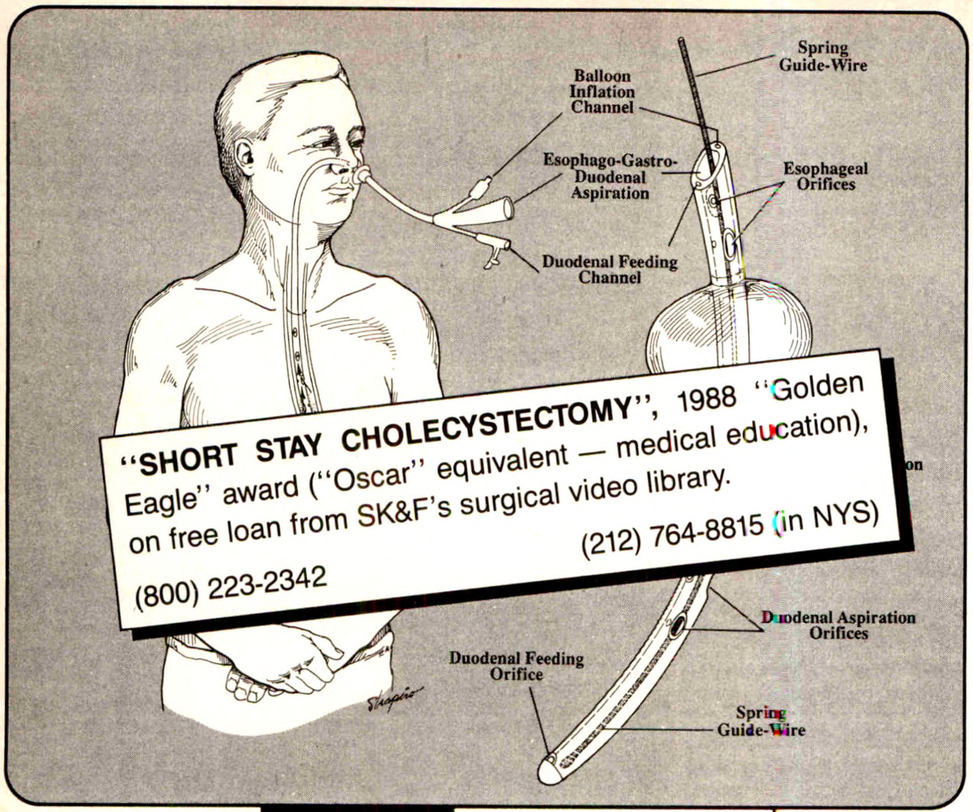

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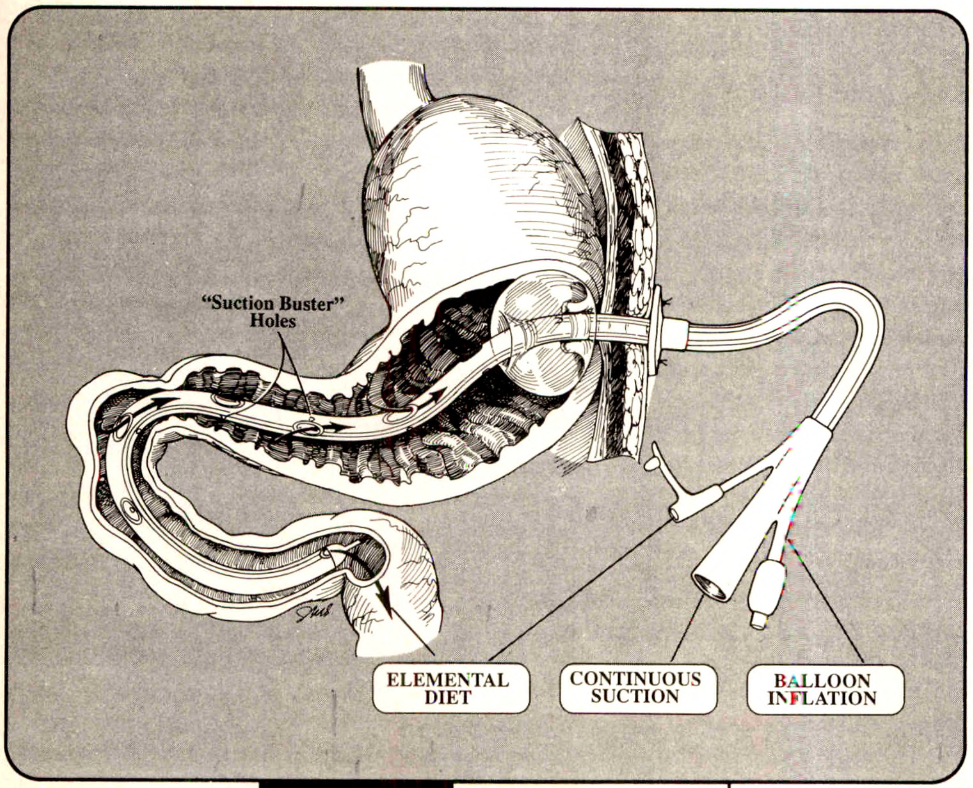

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Charlottesville, Virginia

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Abraham Shaked, M.D., PH.D., John O. Colonna, M.D., Leonard Goldstein, M.D., and Ronald W. Busuttil, M.D., PH.D.
Los Angeles, California

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Arnold G. Diethelm, M.D., David A. Laskow, M.D., Sharon L. Hudson, M.B.A., Mark H. Deierhoi, M.D., W. Henry Barber, M.D., Bruce O. Barger, PH.D., Bruce A. Julian, M.D., Robert S. Gaston, M.D., and John J. Curtis, M.D.
Birmingham, Alabama

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Christopher B. Davies, M.D., J. Wesley Alexander, M.D., SC.D., Barry R. Cofer, M.D., M. Roy First, M.D., and Timothy J. Schroeder, M.S.
Cincinnati, Ohio

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T. Jeffery Wieman, M.D., F.A.C.S., Gareth D. Griffiths, F.R.C.S., and Hiram C. Polk, Jr., M.D., F.A.C.S.
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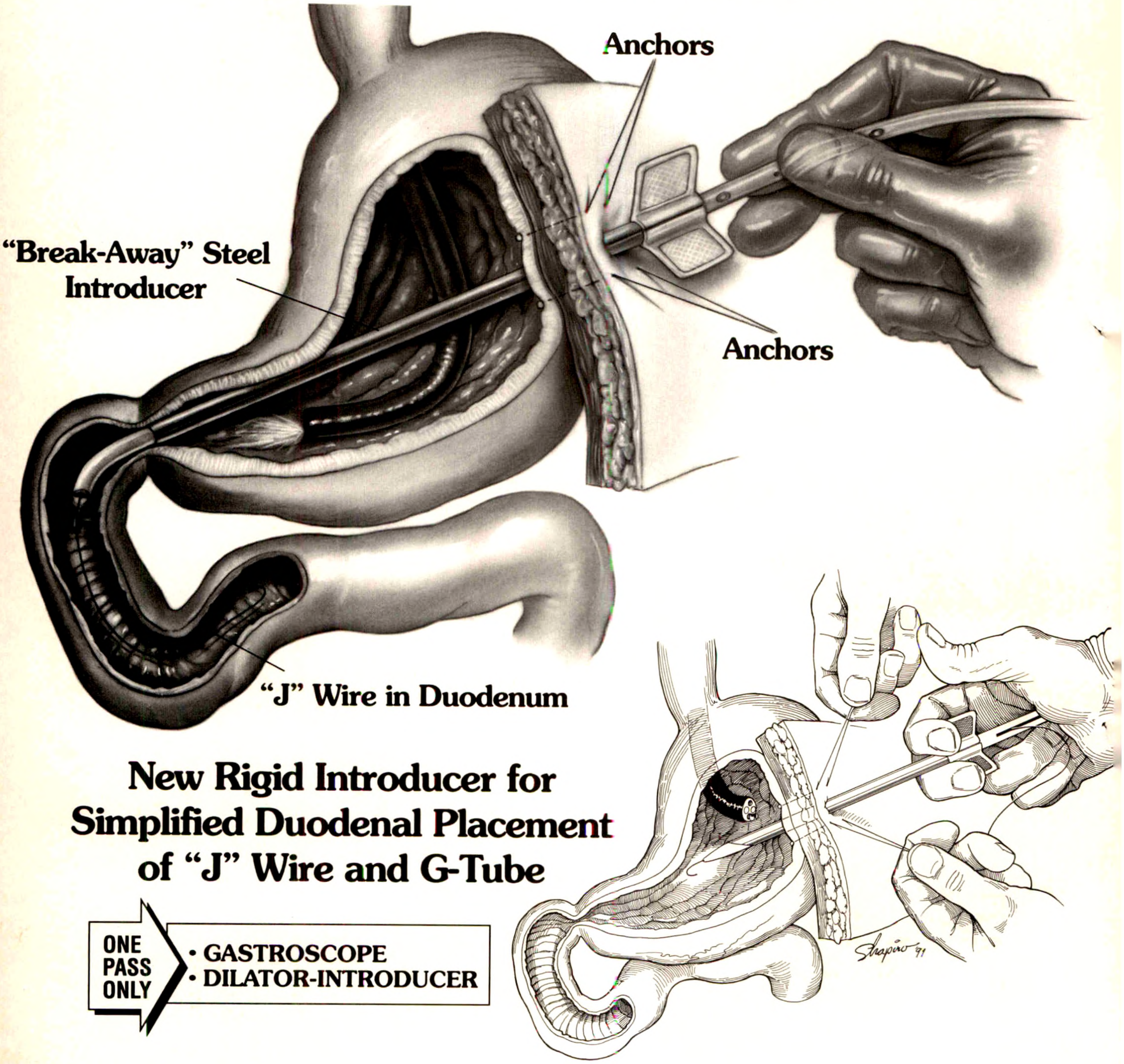

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Greenville, North Carolina, and Rochester, New York

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Kurt Newman, M.D., Judson Randolph, M.D., and Kathryn Anderson, M.D.
Washington, DC

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C. D. Smith, M.D., H. Biemann Othersen, Jr., M.D., Nancy J. Gogan, M.D., and Jennifer D. Walker, M.D.
Charleston, South Carolina

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Carol E. H. Scott-Conner, M.D., PH.D., Terrence J. Hall, PH.D., M.D., Beverly L. Anglin, R.N., and Farid F. Muakkassa, M.D.
Jackson, Mississippi

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Keith D. Lillemoe, M.D., Charles J. Yeo, M.D., Mark A. Talamini, M.D., Bernadette H. Wang, B.S., Henry A. Pitt, M.D., and Thomas R. Gadacz, M.D.
Baltimore, Maryland

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Richmond, Virginia

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Harold J. Wanebo, M.D., R. James Koness, M.D., Peter S. Turk, M.D., and Steven I. Cohen, M.D.
Providence, Rhode Island

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William M. Mendenhall, M.D., Kirby I. Bland, M.D., Edward M. Copeland, III, M.D.,
Glenn E. Summers, M.D., William W. Pfaff, M.D., Wiley W. Souba, M.D., and Rodney R. Million, M.D.
Gainesville, Florida

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Is There a Field of Wound Pharmacology?

Major improvements in almost all branches of surgery have occurred during the past 50 years. Pioneering developments in cardiovascular surgery, organ transplantation, and in the repair of congenital anomalies, to name but a few, are now embedded in everyday surgical practice. Driven by technological advances as well as by new science, this progress has permitted surgeons to restore to health patients who were previously untreatable. These advances also have allowed smoother recovery and reduced morbidity rates for those undergoing conventional operative procedures.

Progress in improving wound healing *per se* has been more moderate. It has centered mainly on the prevention of vitamin, trace metal, and protein deficiencies that delay wound healing or lead to wound breakdown. Beyond attempts to reduce or prevent pathologic scar formation, few active interventions in wound management have fundamentally affected the outcome of healing. Although novel suture materials have been a most important contribution to microsurgery and to vascular surgery, these advances have only marginally affected the healing of surgical wounds and of chronic wounds or ulcerations.

The existence of this relatively static status of wound management has not been for lack of research effort. In fact, in the past two decades we have witnessed elegant studies of the mechanisms of wound healing, not only at the cellular level, but at the biochemical and molecular levels as well. Many of these investigations have been conducted by surgeons in collaboration with basic scientists.[1,2] Until the past 3 to 5 years, however, the conventional wisdom was that for most clean wounds, healing occurred at ceiling rates and by optimal incorporation of cellular and matrix components. Almost no one thought that normal wound healing could be further enhanced by any biochemical or therapeutic manipulation.

The discovery in 1962 of the first growth factor,[3] epidermal growth factor (EGF), did not immediately alter this thinking. More than a decade passed before this growth factor was tested in animal wounds, and it was more than a quarter of a century before the first clinical trial of EGF was reported.[4] Subsequently, other growth factors were discovered and produced in large quantity by recombinant technology. These included platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-β). Once it was recognized that angiogenesis, fibroblast proliferation, and collagen production could be stimulated by these polypeptides, they were applied to experimental wounds.

Thus, it was revealed for the first time that clean surgical wounds could undergo *accelerated* healing. It was soon found that each of these molecules could accelerate healing of chronic wounds or wounds with specific healing deficiencies.[5–7] Because of the many similarities between chronic wounds and chronic duodenal ulcers, accelerated healing of ulcers was also stimulated by administration of an angiogenic factor.[8] Taken together, these results kindled intense activity in university and pharmaceutical laboratories to determine which was "the optimum" growth factor for wounds. The drive to find a single growth factor that could accelerate wound healing was heavily influenced by the potential of clinical application, but also by the added difficulty of obtaining Food & Drug Administration (FDA) approval for mixtures of multiple growth factors. This search for a therapeutic growth factor, however, led to a new concept of "wound pharmacology." The developers of this young field have begun to recognize that optimum promotion of wound healing may require the administration of more than one growth factor.[9] Nevertheless, these efforts have been focused almost exclusively on acceleration of wound healing.

In this issue of the *Annals,* Adzick and Longaker[10] now propose that the field of wound pharmacology deserves a wider focus. They argue that it may soon be possible to therapeutically modify other characteristics of wound healing, for example, scar formation. Such therapy could prevent or reverse many types of pathologic scars, including hepatic cirrhosis, pulmonary fibrosis, and burn contractures. The authors base this proposal on their own studies of fetal wound healing. Fetal wounds in animals and humans heal with greatly diminished scar formation. In its simplest form, the Adzick-Longaker hypothesis says that at least one essential difference between fetal and adult wounds is the level of hyaluronic acid. Fetal wounds heal with a persistently elevated level of hyaluronic acid. Hyaluronic acid in the wound matrix may organize the deposition of collagen in a unique fashion so that little or no scarring or contraction ensues. In contrast, adult wounds have only a transient elevation of hyaluronic acid. The point that should be emphasized is that a thorough understanding of the mechanisms of fetal wound healing may provide a novel approach to prevent pathologic scar formation in adult wounds. The authors quote interesting preliminary experiments in which topical hyaluronic acid was able to modify scar formation in animals. It is also interesting that different fragments of hyaluronic acid can either stimulate or inhibit angiogenesis.[11,12]

It often matters less that a hypothesis is right or wrong, than that it is fruitful. The hypothesis presented here is important especially because it is likely to be very productive for the field of wound pharmacology. As this field develops, it may introduce the next revolution of fundamental advances in surgery.

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Scarless Fetal Healing

Therapeutic Implications

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The purpose of this report is to call attention to the fetal wound healing process as a blueprint for ideal tissue repair. Wound healing in the fetus is fundamentally different from healing in the adult. Fetal tissue repair occurs rapidly and in the absence of scar formation. Because scarring and fibrosis dominate some diseases in every area of medicine, an understanding of fetal wound healing should help develop therapeutic strategies to avert the devastating consequences of excessive scar formation.

RECENT EXPERIMENTAL AND clinical evidence suggests that the fetus responds to injury in a fashion fundamentally different from the adult. Fetal skin wound healing occurs rapidly and in the absence of scar formation. This phenomenon was first observed clinically during the fetal surgery experience at the Fetal Treatment Program of the University of California, San Francisco.[1] Since 1981, 28 human fetal operations have been performed at 18 to 28 weeks' gestation for anatomic defects that have progressive, deleterious physiologic effects during pregnancy and life-threatening consequences after birth, for example, congenital diaphragmatic hernia,[2] severe bilateral obstructive uropathy,[3] congenital cystic adenomatoid malformation of the lung,[4] and sacrococcygeal teratoma.[5] Recent experimental work in a variety of fetal animal models supports the clinical observation of scarless fetal healing. Acute inflammation is virtually absent, hyaluronic acid is a prominent component of the wound matrix, and collagen is deposited in a highly organized, scarless manner. Ongoing research is beginning to unravel the mechanisms that endow the fetus with its unique healing qualities.[6]

The fetal wound healing process may represent a paradigm for ideal tissue repair. The therapeutic goal is to apply the lessons that the fetus is teaching us about wound healing to control the quality of healing. This lodestar may provide the tools for the surgeon to regulate each step of the adult wound healing process: re-epithelialization, inflammation, angiogenesis, contraction, and extracellular matrix synthesis, deposition, and remodeling. Pare's humble statement from over four hundred years ago that "I dressed the wound, and God healed it" may finally be outdated.

The emerging field of "wound pharmacology" is replete with papers that focus on the effect of vulnerary agents, such as growth factors, on wound healing *acceleration.*[7,8] Peacock points out that this approach is far too confining: "To limit our interest in healing to the speed of its various reactions is almost as restrictive as it would be to continue embryological investigation in the hope that a baby can be produced in less than 9 months."[9] With the exception of chronic nonhealing wounds and bone repair, the time required to reestablish tissue continuity and tensile strength after injury is usually not the major clinical issue. Of far greater importance is the restoration of normal tissue structure and function without scar formation.

The Consequences of Scar Formation

Scarring and fibrosis dominate some diseases in virtually every branch of medicine and surgery. For example, the surgeon confronts the consequences of excessive scar formation daily. Skin incisions heal with scar, and sometimes pathologic processes such as keloids and hypertrophic scars are the unanticipated sequelae. Abdominal surgery invariably leads to intraperitoneal fibrous adhesions, and repeated bouts of mechanical intestinal obstruction can result. Strictures occur at anastomotic sites, whether of the bowel, blood vessel, trachea, ureter, or bile duct. The pediatric surgeon is frustrated with the tragic

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problem of biliary atresia in babies—a progressive, fibrotic obliteration of the hepatobiliary tree. Other examples include esophageal stricture after caustic ingestion, post-traumatic urethral stricture, tendon adhesions after hand surgery, and transmission loss after peripheral nerve injury.

Pathologic scarring and fibrosis also frequently occur in nonsurgical specialties. The ophthalmologist observes retrolental fibroplasia in premature infants as well as a similar fibrotic retinopathy in diabetics. The gastroenterologist attempts to mollify the bleeding, liver failure, and encephalopathic complications of hepatic cirrhosis. The pulmonologist detects bronchopulmonary dysplasia in the tiny premature baby and diagnoses pulmonary fibrosis in the aging cigarette smoker. The radiotherapist worries about radiation-induced fibrosis. The cardiologist wishes to ameliorate the fibrotic endpoints of rheumatic heart disease—shortened, distorted chordae and scarred valve leaflets. The dermatologist deals with scleroderma. And this is only a partial list.

All of these problems are notoriously difficult to prevent or treat. The clinician's therapeutic role is largely to "hope for the best," much as physicians did in the past when confronted with what were then unsolved problems: appendicitis until 100 years ago, bacterial infections until 50 years ago, and organ replacement until recently. An understanding of fetal wound healing may lead to therapeutic strategies to help avert scarring and fibrosis. Healing without scar would have a tremendous impact on both medical and surgical practice.

Differences in the Fetal and Adult Wound Environment

The mechanisms that underlie scarless fetal tissue repair are unknown, but may be unique to fetal cells, the fetal wound environment, or a combination of both. The fetal wound environment is quite different from the wound environment after adult tissue injury. The fetus is relatively hypoxemic, with an arterial Po_2 of 20 mmHg,[10] which is lower than the arterial Po_2 of a maskless mountaineer on top of Mount Everest.[11] There is only a minimal inflammatory response to fetal injury, because polymorphonuclear leukocytes and immunoglobulins are not present in the fetal wound matrix.[12,13] Finally, fetal skin wounds are continually bathed in warm, sterile amniotic fluid known to be rich in growth factors that are crucial for development.[14]

The lower fetal oxygen tension, the absence of acute inflammation, and the amniotic fluid environment each might dramatically influence wound healing. But the contribution of these differences to tissue repair may be discounted partially by recent results from fetal animal studies. Fetal tissue oxygenation remains consistently low throughout gestation, yet there is a spectrum to fetal wound healing as a function of gestational age: skin wound healing in the rat or the lamb fetus becomes adultlike with scar formation late in gestation.[12,15,16] Although the absence of polymorphonuclear leukocytes in the fetal wound matrix suggests that some of the characteristic inflammatory mediators of adult wound healing may be absent in fetal wounds, Simpson and Ross[17] have shown that elimination of neutrophils in guinea pig wounds does not diminish scar formation. Several lines of evidence suggest that amniotic fluid exposure is not crucial for scarless tissue repair. At birth, the opossum is physiologically and anatomically a fetus, and remains attached to the mother's nipple for 4 to 5 weeks before weaning. Although the "fetal" development of the marsupial continues in the nonsterile environment of the pouch/nipple and in the absence of an amniotic fluid milieu, scarless skin healing still occurs.[18] Fetal lamb studies have shown that exclusion of wounds from amniotic fluid by a Silastic patch does not obviate scarless repair,[19] and that adult skin transplanted to the fetus heals with scar formation despite exposure to the fluid intrauterine environment.[20]

The Fetal Wound Extracellular Matrix

Scarless fetal wound healing may be attributed to the organization of a unique extracellular matrix (ECM). The fetal ECM has an entirely different profile of macromolecular structural constituents compared with adult ECM. In particular, the early appearance and prolonged maintenance of an environment rich in hyaluronic acid (HA) facilitates cell mobility, cell proliferation, and regeneration in fetal wounds.[21,22] Hyaluronidase-treated polyvinyl alcohol sponges that are implanted into fetal rabbits show a significant reduction in HA content with concomitant striking fibroblast infiltration and collagen deposition.[23] Fetal serum, amniotic fluid, wound fluid, and a number of fetal tissues contain a glycoprotein called hyaluronic-acid–stimulating activity (HASA).[24–26] This factor is present in the fetal wound for a prolonged period, which results in a prolonged HA-rich response in fetal wounds, a mechanism entirely absent in the adult wound.

Studies in our laboratory have examined the mechanisms by which HA is deposited in such abundance in the fetal wound, delineated the nature of fetal wound collagen deposition, and compared these processes with adult wound healing. Based on these studies, a theoretical model of HA deposition in wounds can be proposed. In the adult wound, the early deposition of HA occurs through the platelet plug and the fibrin clot.[27] After the initial deposition of HA, hyaluronidase is produced, HA is removed, sulfated glycosaminoglycans then are deposited, and finally collagen is laid down in a scar pattern (Fig. 1). In contrast, fetal wounds are characterized by a persistent presence of HASA, which underlies the prolonged pres-

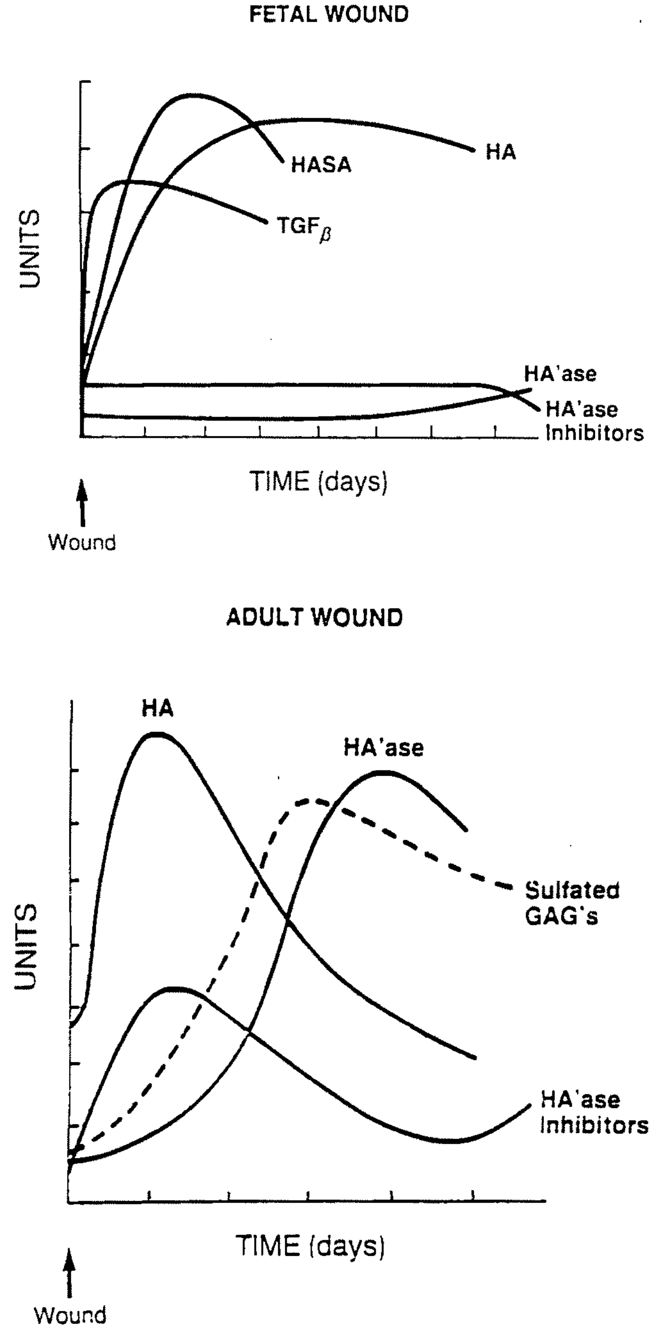

FIG. 1. Conceptualized drawing for the mechanism of hyaluronic acid (HA) deposition in fetal and adult wounds. (A, top) In fetal wounds, hyaluronic-acid-stimulating activity (HASA) rises before HA, and the sustained elevation of HASA underlies the prolonged presence of HA. In a cell culture system, transforming growth factor-beta (TGF-β) stimulates HASA production from fetal fibroblasts. (B, bottom) In contrast, HASA is not present in adult wounds at any time. HA is present only initially and is subsequently degraded by hyaluronidase (HA'ase). The role of hyaluronidase inhibitors (HA'ase inhibitors) in fetal and adult wound healing remains to be determined.

ence of HA. Thus, the mechanism for eliciting the early HA-rich response in adult wounds is entirely different from the prolonged HA-rich response in fetal wounds.

Although the precise mechanisms of action of HA in fetal wound healing are unknown, an HA-rich ECM may provide a permissive environment for the orderly deposition of collagen.[12,24] The deposition of collagen without scarring in the fetal lamb model has been firmly established using histologic, immunohistochemical, biophysical, and biochemical techniques.[28] Siebert et al.[29,30] have postulated that HA influences the reorganization of wound collagen by acting as a carrier for biologically active proteins. In addition, several proteins recently have been isolated from the ECM and found to be able to bind HA; they appear to be involved in the structuring of the ECM.[31,32]

Modulation of Adult Tissue Repair

What is the evidence that adult wounds can be modulated by HA to heal in a fetal-like manner? Historically, it is intriguing that reports from over 50 years ago documented that application of "embryonic tissue juices" enhanced wound repair.[33] Radaelli et al.[34] investigated the effect of HA on wound healing in rats and found that treated wounds develop greater wound breaking strength than untreated controls.[34] This finding was attributed to an early deposition of organized collagen fibers. Hellstrom and Laurent[35] studied the healing of experimental tympanic membrane perforations in rats treated with topical HA. Membranes treated with HA not only close faster than the untreated controls, but also show much less scar tissue, with a discernible organized collagen fiber layer. The healing rate and degree of scar tissue were dependent on the concentration of HA, not on the molecular weight of HA. Abatangelo et al.[36] reported that topical HA enhances epithelial migration in wounded diabetic rats. Balasz and Denlinger[37] postulated that hyaluronate gels are ideally suitable as viscosurgical implants to prevent postoperative adhesions and to control scar formation. Other experimental studies confirm the impression that HA is associated with healing that results in less scarring.[38,39] The efficacy of applying agents to maintain an HA-rich wound environment by either stimulating the deposition of HA or retarding HA breakdown must be tested.

Immunocytochemistry, *in situ* hybridization, and wound fluid analysis should help elucidate the unique growth factor and ECM molecular profile of fetal tissue repair. For example, the deposition of fibronectin and tenascin occurs early in the fetal wound matrix, and these phenomena may underlie rapid re-epithelialization in fetal wounds.[40,41] Recent documentation of the predominance of an embryonic pattern of fibronectin splicing during wound healing in the adult rat suggests that this fibronectin type is functionally more appropriate for the cell migration and proliferation associated with tissue repair.[42] When applied topically, fibronectin expedites wound healing in rats[43] and promotes healing of human corneal ulcers.[44] Although there has been a considerable rush to document the therapeutic efficacy of various peptide growth factors on adult tissue repair, the characteristics of the normal growth environment in adult wound healing have been largely ignored. Preliminary studies examining the profile of peptide growth factors in fetal *versus* adult sheep wound fluid have already shown dramatic differences in insulin-like growth factor II and transforming growth factor-beta isoform levels.[45]

Fetal wound healing research also may permit control of wound contraction. Wound contraction is the process by which the surrounding uninjured tissue is pulled over an open wound defect. When the cicatrization process continues after completion of wound closure, pathologic scar contracture results. Scar contracture can compromise tissue architecture and anatomic function—burn wound contracture and anastomotic stricture are two clinical examples. *In vitro* studies on fetal wound contraction have shown that amniotic fluid can inhibit (rabbit or human)[46,47] or stimulate (lamb)[48] fibroblast-populated collagen lattice (FPCL) contraction. Additional studies *in vivo* are needed to determine whether adult wound contraction can be modulated when exposed to amniotic fluid. Recently, a protein has been identified in sheep amniotic fluid that specifically stimulates human FPCL contraction.[49] Development of antibodies against this protein or isolation of a contraction inhibitor from human amniotic fluid may have substantial clinical utility in preventing scar contracture.

The Fetal Cleft Lip Dilemma

Recently there have been several articles and editorials advocating surgical correction of cleft lip *in utero*.[50–53] Anticipated benefits of this form of surgery would be: (1) restoration of normal lip form without visible scarring, (2) normal midfacial growth unrestricted by scar formation, and (3) prevention of secondary nasal deformities associated with cleft lip. But if fetal surgery is to be effective, the optimal time during gestation when surgery should be performed must be determined. In the fetal lamb model, there is a change to a more adult type of healing with scar formation during the third trimester.[12] In humans, the precise time at which this transition from fetal to adult-type repair occurs is unknown. In addition, human embryos show evidence of secondary deformities associated with clefting beginning at 10 weeks' gestation.[54] Repair later in gestation may partially correct these deformities, but repair during the first trimester may be necessary to provide complete correction.

Advances in prenatal diagnosis, particularly ultrasound, have led to fetal surgery becoming a reality. Diagnosing cleft lip and palate ultrasonographically is not difficult, but there is evidence that the rate of severe defects associated with cleft lip and palate is much higher in clefts diagnosed *in utero* compared with those diagnosed at birth.[35] Thus, the prenatal assessment also must ensure that the fetus found to have a cleft does not have other significant anatomic or chromosomal anomalies.

Fetal surgery for cleft lip and palate carries the same fetal and maternal risks as does surgery for life-threatening fetal anomalies, whereas the benefits, although potentially substantial and attractive, are unproven. Further experimental studies on fetal wound healing and new developments in fetoscopic surgery may eventually allow *in utero* repair of cleft lip and palate. At present, performance of fetal surgery for human clefts is inappropriate.

Summary

Using the fetal wound healing "blueprint," novel guidelines for scarless tissue repair may be defined. Adult wound healing is a complex process involving a variety of cell types, serum components, and cell products. The constituents of fetal wound healing require analysis to understand the control mechanisms that endow the fetus with unique healing abilities. The ultimate aim is to understand the biology of fetal tissue repair, and then to apply these lessons to prevent fibrosis and contracture in children and adults.

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ORIGINAL ARTICLES

Curative Resection in Zollinger–Ellison Syndrome

Results of a 10-Year Prospective Study

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Since 1980, 73 patients with Zollinger–Ellison syndrome (ZES) without radiographic evidence of liver metastases were studied on a prospective protocol including medical management of gastric acid hypersecretion, extensive radiographic tumor localization, and exploratory surgery to find and resect gastrinoma for potential cure. Each patient had gastric acid hypersecretion effectively controlled with either H_2-blockers or omeprazole. Patients were divided prospectively into two groups, with all patients undergoing the same preoperative localization studies and extensive laparotomy. In contrast to group 1 (1980–1986) (36 patients), group 2 (1987–Oct. 1990) (37 patients) also underwent additional procedures (transillumination and duodenotomy) at surgery to find duodenal gastrinomas. Preoperative imaging studies localized tumor in 38 (52%) patients, and portal venous sampling for gastrin determinations was positive in 49 (67%) patients. Gastrinomas were found and resected in 57 (78%) patients. Significantly more gastrinomas (92% of patients) were found in group 2 than in group 1 patients (64%) ($p < 0.01$). This increase was due to increased numbers of duodenal gastrinomas in group 2 than in group 1 patients (43% *versus* 11%; $p < 0.01$). The increased ability to find duodenal gastrinomas did not significantly improve the immediate disease-free rate, which was 58% for all patients. Duodenal primary gastrinomas were found to have a significantly greater incidence of metastases (55%) and a significantly shorter disease-free interval (12 months) than pancreatic gastrinomas (22% and 84 months, respectively) suggesting that duodenal gastrinomas may be more malignant and not more frequently curable than pancreatic gastrinomas. Operations were performed with no deaths and 11% morbidity rate. Long-term follow-up showed that 50% of patients initially rendered disease free would develop recurrent disease by 5 years. Survival was excellent for all patients, and none died of malignant spread of the tumor or uncontrolled peptic ulcer disease, with a mean follow-up of 5 years. This finding is in contrast to patients who presented with metastatic disease on imaging studies and had a 20% 5-year survival rate. This study suggests that all patients with localized sporadic ZES can have the gastric acid hypersecretion managed medically, that overall survival of these patients is excellent, most (78%) can have all gastrinoma found and resected, and some (30%) will be cured (long-term disease-free survival).

THE ZOLLINGER–ELLISON SYNDROME as originally described was clinically characterized by severe peptic ulcer disease associated with profound gastric acid hypersecretion in the presence of a non-beta islet cell tumor of the pancreas,[1] which now is known to be secondary to ectopic release of gastrin by the tumor. Since its original description, it has been apparent that all patients have two fundamental aspects of their disease that must be managed: the profound gastric acid hypersecretion and the malignant nature of the gastrinoma.[2-11]

Initially, attention was primarily directed at controlling the life-threatening gastric acid hypersecretion, which, if left improperly treated, led to perforation and hemorrhage.[1,3,4] For many years, total gastrectomy was the only effective treatment for the gastric acid hypersecretion because resection of the gastrinoma was almost always not successful.[1,3,4,8] In the last few years, however, with the availability of progressively more potent gastric antisecretory agents, medical control of gastric hypersecretion has become increasingly more effective.[5,11-17] With the recent availability of H^+-K^+-ATPase inhibitors such as omeprazole, gastric hypersecretion can now be controlled in all patients, and it is recommended that total gastrectomy currently be used only in the rare patient who can not or will not take oral antisecretory drugs.[5,11,15-18]

In contrast to the control of the gastric acid hypersecretion, where great progress has been made and there is general agreement in the treatment approach, the ap-

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proach to the gastrinoma remains unclear and controversial.[9,10,18] Because gastrinomas, unlike insulinomas, but similar to glucagonomas, VIPomas, somatostatinomas, PPomas, or GRFomas, are malignant in 60% to 90% of patients in older studies,[3,4,11,19,20] most authorities agree that effective surgical treatment needs to be developed.[6,7,9,11,21,22] This view is reinforced by the fact that 60% of all patients in long-term studies in which acid hypersecretion is controlled died of the malignant nature of the disease,[2,3,23] demonstrating that it will become the main determinant of long-term survival. Many physicians still have reservations about sending these patients for routine surgical exploration, however, because of varied surgical results. Authorities have varied from recommending routine surgical exploration to recommending that routine surgical exploration not be done.[5,9,10,18,22,24–30] The primary reason for this difference of opinion in approach to the gastrinoma is that surgical cure rates have varied from 5% to 35% in different series[2,5,6,7–11,22,24–28,30,31] and even up to 82% in a recent study,[29] and the results have been limited in various studies because of a number of features. First, even in recent series because of the uncommonness of the disease the number of patients in the series is small and the studies often are not prospective in nature. Second, the follow-up is often short, and provocative tests are not routinely done to assess true long-term disease-free survival. Third, often the most advanced imaging studies as well as other, newer localization studies are not performed, so that it is not apparent whether a better cure rate could have been obtained with state-of-the-art localization studies. Fourth, in almost all older series, a significant percentage of patients had total gastrectomy, in contrast to the present, where it is now rarely needed. Because gastrinomas in some recent studies in up to 40% of cases are duodenal in location[11,21,29,32] and would frequently be removed by chance with the resected gastroduodenal segment, the true cure rate without such blind resection, which is not done today, is not established.

The aim of the present study was to address each of the inconsistencies reviewed above and to attempt to define the ability to localize gastrinomas and surgically cure patients with Zollinger–Ellison syndrome. This was accomplished by a 10-year prospective study examining the ability to surgically cure 73 consecutive patients with Zollinger–Ellison syndrome who had no evidence of the multiple endocrine neoplasia type 1 syndrome or metastatic disease by imaging studies.

Materials and Methods

Since 1980, 121 consecutive patients were referred to our institution with a diagnosis of Zollinger–Ellison syndrome and studied according to an approved protocol. The diagnosis of Zollinger–Ellison syndrome was initially confirmed in each patient by measuring fasting serum gastrin concentration, the increment in serum gastrin level in response to 2 U/kg of a bolus injection of intravenous (I.V.) secretin and an I.V. calcium infusion (5 mg/kg/hour calcium × 3 hours) and the basal and pentagastrin-stimulated maximal acid output as previously described.[11,32–35]

The diagnosis of Zollinger–Ellison syndrome was confirmed if at least two of the following three criteria were present: elevated fasting serum gastrin level > 100 pg/mL, basal acid output greater than 15 mEq/hour if the patient had had no previous gastric surgery, or greater than 5 mEq/hour if the patient had had prior gastric surgery, and an increase in serum gastrin level of 200 pg/mL after the I.V administration of secretin, or 395 pg/mL after an I.V. calcium infusion.[11,32–35]

The oral antisecretory drug dosage requirement was determined for each patient, as described previously,[11,35,36] and was defined as the amount of antisecretory drug required to suppress acid output < 10 mEq/hour in the final hour before the next scheduled dose of medication. If the patient had had prior gastric surgery, then a dose of medication to reduce acid output to <5 mEq/hour was determined.[5,11,35–37] A parenteral antisecretory drug dose to control gastric acid output at the time of surgery was determined as described previously in all patients.[38–40]

All patients (n = 121) underwent upper gastrointestinal series, upper gastrointestinal endoscopy, computed tomography, ultrasound, and selective hepatic, gastroduodenal, splenic, and superior mesenteric arteriography.[32,41–44] Since 1987, patients also underwent magnetic resonance imaging (MRI) of the abdomen and liver.[45]

Patients with evidence of liver metastases on imaging studies that could have biopsies done percutaneously or laparoscopically (n = 18) were excluded from this study and placed on protocols for advanced disease.[46,47] Patients with evidence of multiple endocrine neoplasia type I (n = 22), in whom routine surgical exploration is not generally recommended,[5,11,18] were excluded from this study and placed in a separate protocol.[48,49] Patients with severe concomitant medical problems (n = 8) (severe cardiac disease [n = 2], chronic obstructive lung disease [n = 1] or advanced liver disease [n = 5]) that precluded surgery were excluded. All remaining patients (n = 73) underwent percutaneous transhepatic venous sampling of the portal vein and its tributaries for gastrin levels before surgery,[50] and 18 patients since 1988 underwent secretin injections of selective arteries and measurement of gastrin levels in hepatic venous or other venous samples to localize the gastrinoma during arteriography, as described recently.[51]

The results of the radiographic imaging and localizing studies were available to the operating surgeon. Surgery was performed in the last 67 cases by one surgeon (JAN) and in the first six cases by another surgeon (JWH).[33] On the basis of the type of exploration done, patients were prospectively divided into two groups, and the results from each group were analyzed separately. Group 1 consisted of patients from 1980 through 1986 (36 patients) who underwent the standard extensive laparotomy briefly outlined below. Patients in group 2 underwent exploration from 1987 through October 1990 (37 patients), and these patients underwent an identical standard extensive laparotomy to patients in group 1, but in addition, an enhanced search for duodenal gastrinomas using transduodenal endoscopic illumination[52] and duodenotomy. Briefly, in the standard extensive laparotomy,[32] the liver, pelvis, small intestine, pancreas, stomach, duodenum, mesenteric, and retroperitoneal regions in the upper abdomen were explored. The pancreatic head and duodenum were exposed and mobilized by performing an extended Kocher's maneuver that included mobilizing the ascending colon and hepatic flexure. The pancreatic body and tail were inspected and palpated by opening the gastrocolic ligament and exposing the lesser sac. The splenic flexure of the colon was also mobilized to facilitate inspection and palpation of the pancreatic tail, and all women had careful palpation of the ovaries. After complete operative exposure and careful palpation, since 1982 each patient (n = 62) underwent intraoperative ultrasound using a 10-MH$_z$ real-time transducer as previously described.[53] Patients in group 2, in addition, underwent intraoperative endoscopic transillumination of the duodenum, performed as described previously,[52] with or without duodenotomy[21] to more carefully examine the duodenum for any evidence of small duodenal gastrinomas not detected by the other methods. Briefly, intraoperative endoscopic transillumination was performed by passing an upper gastrointestinal endoscope orally at the time of surgery and carefully transilluminating the duodenum. Biopsies were performed on all abnormalities seen by the endoscopist or that failed to transilluminate.[52] A 3-cm duodenotomy was performed along the antimesenteric aspect of the duodenum centered on the second portion of the duodenum with the option to extend in either direction. The duodenal wall was carefully palpated with the index finger inside the duodenum and the thumb on the outside, and the distal third and fourth parts of the duodenum were examined similarly by everting them into the incision. Any suspicious pancreatic, gastric, liver, duodenal, bowel, or peripancreatic nodule or lymph node that was identified by any method (palpation, intraoperative ultrasound, transillumination) was removed for pathologic analysis. In the bowel or stomach wall, a suspected tumor was excised with a full-thickness rim of normal gut around the tumor. In the pancreatic head or adjacent lymph node areas, suspected tumors were excised. In the distal pancreas, suspected tumors were resected along with the surrounding pancreas and spleen. In one patient, an ovarian cystadenocarcinoma was identified, and this patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. If a gastrinoma was not found, no gastric or pancreatic resection was performed.

After surgery, before discharge, each patient underwent determination of fasting serum gastrin level and the change in serum gastrin level after secretin provocation performed as described previously.[32] Each patient was discharged on the same dose of antisecretory drug as preoperatively. Patients then were re-evaluated at 3 to 6 months postoperatively and then yearly for evidence of tumor recurrence and control of gastric hypersecretion.[29,32] At the 3- to 6-month follow-up, tumor recurrence was assessed by noninvasive imaging studies (ultrasound, MRI scan, computed tomography [CT] scan), selective abdominal angiogram, and functional studies (fasting gastrin concentration, secretin and calcium provocative studies, basal acid output).[29] The criteria for disease-free survival of patients with Zollinger–Ellison syndrome were: (1) normal fasting serum gastrin concentration (<100 pg/mL), (2) a negative secretin- (<200 pg/mL increase) and calcium-provocative test (<395 pg/mL increase),[34] and (3) no evidence of tumor on follow-up imaging studies

Disease-free survival and survival were graphed by the Kaplan-Meier method and analyzed for significant differences by the Breslow modification of the Kruskal-Wallis test. Proportions were compared by the Fisher's exact test. Differences with $p < 0.05$ were considered significant.

Results

Patient Characteristics, Medications, and Localization Studies

Seventy-three patients were entered prospectively into this study. Fifty patients were men, and 23 patients were women (Table 1). The mean age of all patients was 49 years. Twenty-six patients (36%) had had prior upper abdominal surgery, including either partial gastrectomy or vagotomy in most these patients. There was a mean time of 8 years between the onset of symptoms and the diagnosis of Zollinger–Ellison syndrome, and one patient had symptoms of peptic ulcer disease for 35 years before the diagnosis of Zollinger–Ellison syndrome.

The basal acid output was markedly elevated in all but five patients who had had prior subtotal gastrectomy and vagotomy, and the mean basal acid output for all patients was 58 mEq/hour (Table 1). In most patients, the serum gastrin level was markedly elevated, with a mean fasting serum gastrin concentration of 909 pg/mL. All but five patients had an abnormal serum gastrin response to secretin or calcium provocation, with a mean increment of 1669 pg/mL and 424 pg/mL, respectively.

Each patient preoperatively had the gastric acid output successfully controlled by oral antisecretory medication (Table 1). As the study progressed, we have employed more potent medications, making the control of the acid output progressively easier. As the potency of the antisecretory medication increased,[5,11,36] as is evidenced from Table 1, the dose of antisecretory medication decreased, with a mean cimetidine dose of 6.0 g/day (n = 11); ranitidine, 2.2 g/day (n = 39); famotidine, 0.3 g/day (n = 9); and omeprazole, 84 mg/day (n = 14) (Table 1). Currently, most patients are managed with one daily dose of omeprazole, requiring approximately 60 to 120 mg/day (Table 1).

In 52% of patients preoperative imaging studies demonstrated a gastrinoma. In 67% of patients, a positive gastrin gradient (> 50% increase over simultaneous peripheral sample[50]) on portal venous sampling for gastrin was found. All but two of these gastrin gradients were present in the superior or inferior pancreaticoduodenal vein, suggesting that the gastrinoma was present within either the pancreatic head or duodenum[50] (Table 1). A similar proportion of patients had marked increments in hepatic vein gastrin levels after the injection of secretin into the gastroduodenal artery, suggesting similar localization (data not shown).[51]

Ability to Find Gastrinoma

Gastrinomas were found and resected in 57 of 73 patients (78%) (Table 2). The addition of procedures to more carefully examine for duodenal gastrinomas (group 2) significantly improved the ability to find and resect gastrinomas (Table 2). Specifically, before these procedures, 64% of patients (23 of 36) had gastrinomas removed (group 1, Table 2), whereas subsequently 92% of patients (34 of 37) had gastrinomas excised ($p < 0.01$) (group 2, Table 2). The increase in gastrinomas found in group 2 was entirely due to an increased proportion of duodenal wall gastrinomas excised and not to an increased ability to find gastrinomas in the area of the duodenum, within the pancreas, or in adjacent duodenal lymph nodes (Table 3). Specifically, in the initial 36 patients in group 1, only four duodenal wall gastrinomas were excised. In contrast, in group 2, in which an extensive search of the duodenum was added, 16 of the 37 patients had duodenal wall gastrinomas excised (43%) (Table 3). This difference was significant ($p < 0.01$), and it implied that duodenal wall gastrinomas were likely being missed in the 37% of patients in whom no gastrinomas were found in group 1 (Table 2). The average size of the duodenal gastrinoma in group 2 was 6 mm, with 38% between 1 and 5 mm, and the remainder between 6 and 10 mm, whereas the

TABLE 1. *Preoperative Characteristics, Antisecretory Medication Dose, and Localization Results of Patients With Zollinger-Ellison Syndrome*

								Antisecretory Drug Requirement									
								Cimetidine		Rantidine		Famotidine		Omeprazole		Tumor Localization Studies	
n	Sex M:F	Mean Age (yr) (range)	No. With Previous Upper Abdominal Surgery	Mean Time From Symptoms to Surgery (yr) (range)	Mean Basal Acid Output (mEq/hr) (range)	Mean Fasting Gastrin (pg/mL) (range)	Delta Secretin Gastrin (pg/mL) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	Δ Imaging* Positive	Δ PVS Positive
73	50:23	49 (29–66)	26 (36%)	8 (1–35)	58† (4–159)	909 (133–7000)	1669‡ (67–21700)	11 (15%)	6050 (2400–12000)	39 (53%)	2260 (300–5400)	9 (12%)	308 (80–800)	14 (19%)	84 (60–120)	38 (52%)	49 (67%)

* Imaging includes ultrasound, computerized tomography scan, magnetic resonance imaging scan, and selective arteriogram.

† Five patients had basal acid output <15 mEq/hr, and each had had prior acid reduction surgery, including previous vagotomy and antrectomy.

‡ Seven patients had a less than 200 pg/mL increment in serum gastrin level after the administration of 2 U/kg of secretin IV (negative secretin test result).

PVS, selective transhepatic sampling of the protal vein and its tributaries for serum gastrin determination with a positive gradient equal to or greater than a 50% increase over simultaneous peripheral value as defined in Methods.

TABLE 2. *Ability to Find Gastrinoma as a Function of Intensive Operative Focus on the Duodenum*

	Surgical Group*		
Result of Surgery	I (n = 36)†‡	II (n = 37)‡	Total (n = 73)
Gastrinoma found (n)	23 (64%)†‡	34 (92%)‡	57 (78%)
Gastrinoma not found (n)	13 (36%)†‡	3 (8%)‡	16 (22%)

* Group 1 (1980–1986) and group 2 (1987–October 1990) differed in that patients in group 2 underwent additional procedures to search for duodenal gastrinomas as described in Methods.

† Numbers are the number of patients in the indicated surgical group with the indicated surgical result. Numbers in parentheses are the percentage of patients in the indicated group with the indicated surgical result.

‡ Significant differences betwen group 1 and group 2 by Fisher's exact test ($p < 0.01$).

four duodenal gastrinomas in group 1 had a mean size of 6 mm (range, 4 to 10 mm), with only 1 tumor < 5 mm, suggesting that small duodenal gastrinomas may have been missed in group 1. In group 1, the proportion of patients with pancreatic gastrinomas (33%) was significantly higher than those with duodenal gastrinomas (11%, $p < 0.05$), whereas in group 2, duodenal wall gastrinomas were found in 43% of patients, and the occurrence of these tumors was as common as pancreatic tumors (30%) ($p > 0.1$) (Table 3).

Ability to Cure

Of the 73 total patients explored, 42 patients (58%) at 3 to 6 months had a normal fasting serum gastrin concentration, negative gastrin provocative tests, and negative imaging, and thus were defined as disease free, as outlined in Methods. At the 3- to 6-month follow-up after operation in group 1, 19 of 36 patients (52%) were disease free, which was not significantly different from group 2, with 23 of 37 (62%) patients disease free ($p = 0.5$). Therefore, although the use of extensive duodenal evaluation significantly improved the ability to find and resect gastrinoma (Table 3), it did not significantly improve the ability to render patients disease-free. To further investigate this finding, the ability to render patients disease free was considered as a function of tumor location (Table 4). The 3- to 6-month disease-free rate was similar in patients in groups 1 and 2 for pancreatic gastrinomas (92% *vs.* 73%, $p = 0.5$) and gastrinomas within lymph nodes (83% *vs.* 71%, $p = 1.0$). In addition, the percentage disease free for duodenal gastrinomas was not significantly different in group 2 (62%) and group 1 (50%, $p = 1.0$, Table 4). These results suggest that the failure of the disease-free rate to increase in patients in group 2 (although more tumors were found) was likely not due to a failure to render more patients with duodenal gastrinomas disease-free even though more duodenal gastrinomas were found in group 2 than in group 1 (Table 3). To investigate the basis for this further, the malignant potential (as defined by the presence of pathologically proven lymph node or liver metastases) of duodenal and pancreatic primary gastrinomas was compared. A greater proportion of patients with duodenal gastrinomas had evidence of metastases, 55% *versus* 22%, $p = 0.05$ (Table 5). The higher presence of metastatic disease in patients with duodenal primaries may explain the inability to significantly increase the short-term cure rate in group 2 patients, even though additional gastrinomas were found in this group.

Long-term Follow-up and Survival

To assess long-term disease-free survival, each patient was evaluated yearly. The median follow-up of all patients was 45 months (range, 3 to 120 months). Of the 42 patients who were resected and appeared to be disease free at initial postoperative evaluation, 10 patients have developed evidence of recurrence (Fig. 1, top panel). There appear to be 2 peak periods for the detection of recurrence, one at less than 1 year and the second at 5 years (Fig. 1, top panel). Recurrent Zollinger–Ellison syndrome was manifested by elevated fasting serum levels of gastrin and/or abnormal gastrin provocative testing results only in 6 patients and elevated serum gastrin levels and/or gastrin provocative test abnormalities plus recurrent tumor on imaging studies in 4 patients. The four patients with recurrent gastrinoma on imaging studies were re-resected at 8, 5, 2 and 1 year following the initial procedure and one was again able to be rendered disease-free. These reoperations included excision of gastrinoma from perinephric nodes, liver, duodenum, and adjacent duodenal

TABLE 3. *Location of Primary Gastrinoma in Various Surgical Groups*

	Location of Primary Gastrinomas Resected†		
Surgical Group*	Duodenum‡‖¶	Pancreatic	Lymph Nodes Only
Group 1 (n = 36)	4 (11%)	12¶ (33%)	6 (17%)
Group 2 (n = 37)	16‖ (43%)	11 (30%)	7 (20%)
Both (n = 73)	20 (27%)	23 (32%)	13 (18%)

* Group 1 (1980–1986) and group 2 (1987–October 1990) differed in that patients in group 1 underwent additional procedures to search for duodenal gastrinomas as described in Methods.

† One patient had an ovarian gastrinoma, and 13 patients had no tumor found.

‡ Numbers refer to the number of patients in each group with a gastrinoma found in the indicated location. Numbers in parentheses are the percentage of the total patients in the indicated surgical group with gastrinomas in this location.

‖ Proportion of duodenal gastrinomas found was significantly greater in group 2 *vs.* group 1 patients ($p < 0.01$).

¶ Proportion of pancreatic gastrinomas found in group 1 was greater than that of duodenal gastrinomas found in group 1 ($p < 0.05$)

TABLE 4. *Ability to Initially Surgically Cure Patients With Zolliner-Ellison Syndrome as a Function of Primary Tumor Location*

	Location of Resected Primary Gastrinoma											
	Duodenum			Pancreas			Lymph Nodes			Total		
Group*	No. With Tumor Found	No. Cured†	% Cured‡	No. With Tumor Found	No. Cured	% Cured	No. With Tumor Found	No. Cured	% Cured	No. With Tumor Found	No. Cured	% Cured
I	4	2	50	12	11	92	6	5	83	22§	18§	82
II	16	10	62	11	8	73	7	5	71	34	23	67
Both	20	12	60	23	19	83	13	10	77	56§	41§	37

* Group 1 (1980–1986) (n = 36) and group 2 (1987–October 1990) (n = 37) differed in that patients in group 2 underwent additional procedures to search for duodenal gastrinomas as described in Methods.

† Cure defined as a normal fasting gastrin concentration, negative imaging studies, and negative secretin and calcium provocative tests as described in Methods at a follow-up evaluation 3 to 6 months after operation.

‡ Cure refers to the percentage of patients with a gastrinoma found who were cured.

§ One patient had a primary ovarian gastrinoma and was cured. She is excluded from this analyusis.

nodes. The initial determination at 3 to 6 months postoperatively of no evidence of disease by normal serum gastrin level, negative imaging studies, and normal response to provocative testing did not predict that an individual patient will remain free of disease (Fig. 1, top panel). Long-term follow-up suggests that 50% of patients in this category will develop evidence of recurrent disease at 5 years (Fig. 1, top panel). Furthermore, the tumor recurrence rate long-term did not differ significantly for patients with primary tumors successfully resected from the pancreas or lymph nodes (Fig. 1, bottom panel). Patients with duodenal gastrinomas had a significantly shorter median disease-free interval (12 months) than did patients with pancreatic primary tumors (84 months, p < 0.01) but not those with lymph node gastrinomas (60 months, p = 0.1). Specifically, for patients who were initially found to be disease free with duodenal tumors, the 5-year disease-free rate was only 40%, whereas for patients with pancreatic tumors who were disease free at 3 to 6 months, the 5-year disease-free rate was 70%; similarly, for lymph node gastrinomas it was 60% (Fig. 1, bottom panel).

Of the 16 patients in whom no gastrinoma was found at operation, each patient retained functional evidence of Zollinger–Ellison syndrome, but only one patient has subsequently developed gastrinoma on imaging studies 6 years later. That patient was re-explored and gastrinoma was excised from the pancreas, and the patient is currently disease free. Two patients in this group have died on long-term follow-up (7-year follow-up), but in both cases the death was not related to Zollinger–Ellison syndrome (one death due to metastatic colon cancer, and the other to liver failure) (Fig. 2). Of the 15 patients who had tumor found and resected but were not rendered disease free on functional studies, only one has developed recurrent tumor on imaging study. This patient initially had a pancreatic body gastrinoma, and 3 years later developed a mesenteric lymph node near the ligament of Treitz that was excised, but his serum levels of gastrin remain elevated. Long-term survival (7 years) in this group is excellent (100%) (Fig. 2). Long-term survival of patients disease free at the 3- to 6-month postoperative follow-up was also excellent. In follow-up up to 9 years, only one patient has died of causes unrelated to the Zollinger–Ellison syndrome (cancer of the oropharynx). There are no apparent differences in survival in any surgical group (Fig. 2).

TABLE 5. *Presence of Metastatic Disease* With Duodenal and Pancreatic Primary Lesions*

Location of Primary Gastrinoma	n	No. With Metastases (%)
Pancreas	23	5 (22)
Duodenum	20	11 (55)†

* Metastatic disease was defined as the percentage of tumor in an adjacent lymph node (n = 12) or the liver (n = 4) in patients with a primary gastrinoma at the indicated site in group 1 and group 2.

† A significantly greater proportion of patients with duodenal primary lesions had metastases (p = 0.05).

In contrast to the 73 patients in the current study undergoing surgical exploration with no evidence of metastatic disease on the initial evaluation who had excellent long-term survival (mean survival, 90% at 5 years) (Fig. 2), the 5-year survival in all patients with sporadic disease who did not enter the study because of metastatic gastrinoma was less than 20% (p < 0.001) (Fig. 2).

Complications

Of 79 operations to excise gastrinoma from 73 patients (6 patients were operated on for recurrent or metastatic gastrinoma) with Zollinger–Ellison syndrome, there were no operative deaths, and nine operations (11%) produced complications. Complications included hemorrhage (n = 1), colon injury (n = 1), abscess (n = 2), wound infection

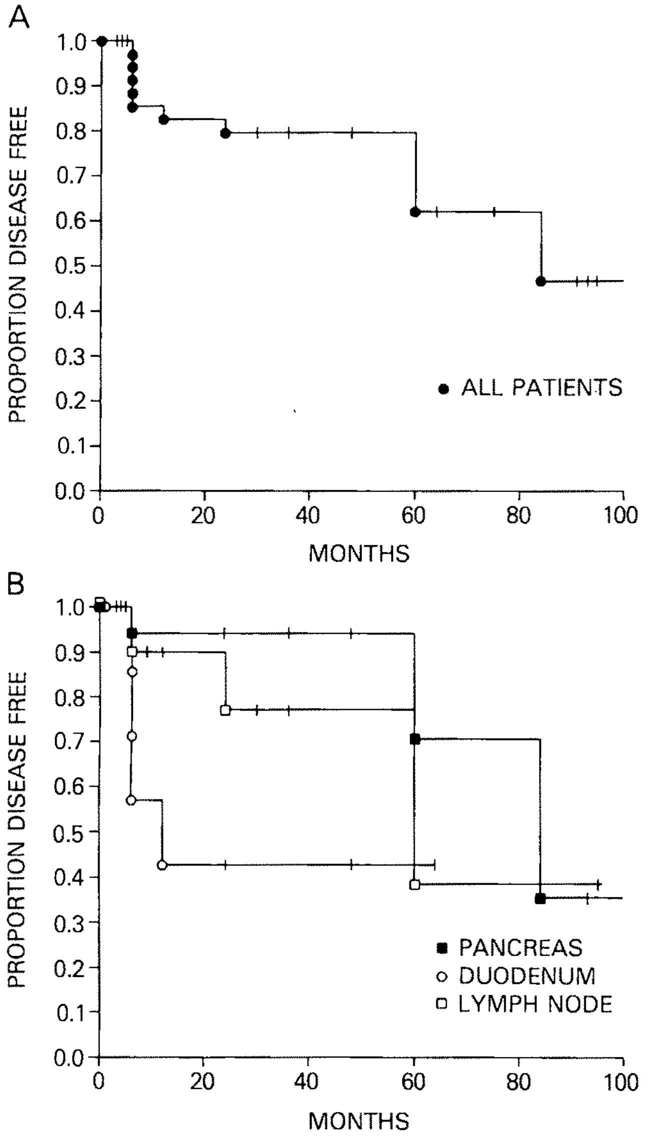

FIG. 1. Time to recurrence of Zollinger-Ellison syndrome in patients initially disease free by surgery. (Top) The Kaplan-Meier plot of the time to recurrence for all patients (n = 42) who were disease free of Zollinger-Ellison syndrome at the initial (either 3- or 6-mo) postoperative follow-up. Disease free is defined as no evidence of gastrinoma on imaging studies, normal fasting gastrin concentration, and negative secretin and calcium provocative tests as outlined in Methods. Recurrent disease has developed in few patients. (Bottom) Kaplan-Meier plot of the time to recurrence of Zollinger-Ellison syndrome of patients who were rendered disease free of Zollinger-Ellison syndrome at the initial postoperative follow-up divided by primary disease site: duodenum (n = 12), pancreas (n = 19), and lymph node (n = 10). One patient with the primary ovarian gastrinoma is excluded. Patients with primary duodenal gastrinomas had a significantly shorter disease-free interval than patients with pancreatic gastrinomas ($p < 0.01$). The differences between patients with duodenal gastrinomas and those with lymph node-only gastrinomas were not significant ($p = 0.1$). The median disease-free survival for patients with duodenal, pancreatic, or lymph node primary gastrinomas was 12, 84, and 60 months, respectively.

(n = 2), pulmonary embolus (n = 1), septic thrombophlebitis (n = 1), duodenal leak (n = 1), and small bowel obstruction (n = 1). One patient had two complications: wound infection and a small bowel obstruction. Of the complications that occurred, six required a repeat surgical procedure. Follow-up suggests long-term sequelae of only one complication, hearing loss and dizziness secondary to the prolonged use of gentamicin to treat an abdominal abscess.

Discussion

When this study was initiated in 1980, a number of advances had occurred that suggested that a prospective study to localize and resect gastrinomas for cure in a large number of consecutive patients would provide results that would clarify the management of the tumor in these patients. With the widespread use of the gastrin radioimmunoassay and secretin provocative testing, the ability to diagnose Zollinger-Ellison syndrome in patients with peptic ulcer disease was greatly facilitated^{54,55} and might lead to the early detection of smaller, more curable gastrinomas. Radiographic methods to localize islet cell tumors also were improving dramatically, including improved CT scanning,^{56,57} subtraction angiographic methods, and improved ultrasound devices. Reports suggested that selective pancreatic arteriography could accurately localize 90% of insulinomas and other islet cell tumors such as gastrinomas, as well as identify metastatic dis-

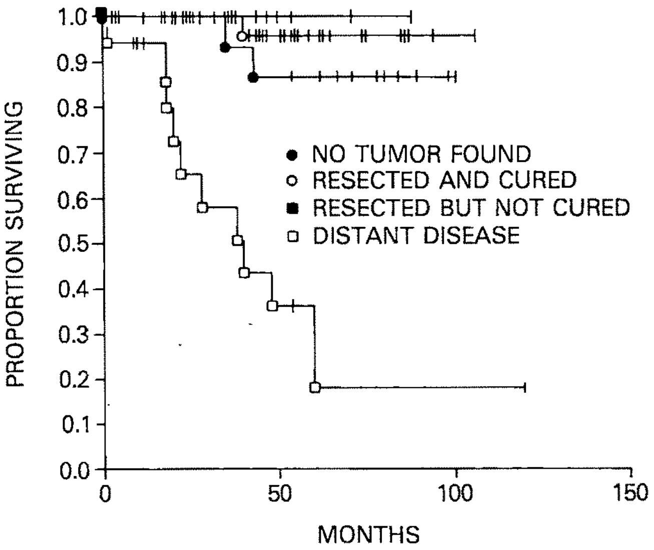

FIG. 2. Survival of patients with Zollinger-Ellison syndrome from the day of diagnosis. Patients were divided into four groups based on preoperative evaluation, operative findings, and initial postoperative evaluation: patients who had biopsy confirmation of bulky metastatic gastrinoma on initial evaluation (n = 18, open squares), patients who had no tumor found during surgery (n = 16, closed circles), patients who had all tumor resected and were functionally disease free (cured) at initial postoperative evaluation (n = 42, open circles), and patients who had all tumor resected but were functionally not disease free (cured) (n = 15, closed squares). There were no significant differences seen among the three groups who did not have metastatic gastrinoma. However, the group with distant disease survived for a significantly shorter time than all other patient groups ($p < 0.001$).

ease.[58–60] Studies suggested that transhepatic venous gastrin sampling from the portal vein and its tributaries could greatly improve localization of gastrinomas.[61,62] Furthermore, with the increased ability to control gastric acid hypersecretion medically in all patients, obviating the need for routine total gastrectomy,[12] it was possible to have time to both perform detailed imaging studies preoperatively and to concentrate on localizing and removing the gastrinoma at surgery. The detailed imaging studies allowed identification of patients without metastatic disease who would possibly benefit from surgery as well as more precise information about the location of the primary gastrinoma.[56,57,59,60] The control of gastric acid hypersecretion preoperatively allowed the effects of long-term gastric acid hypersecretion such as metabolic and nutritional abnormalities to be corrected to reduce the risks of extensive surgery, and allowed detailed surgical exploration directed at the tumor to be carried out without the risks of gastric acid hypersecretion at operation and postoperatively. Earlier attempts to operatively localize and resect gastrinomas were limited[4] because of the lack of good preoperative localization methods that could identify patients who might benefit from surgery and because surgeons had to remove the stomach, a procedure that required a major proportion of the operating time, removing time and energy needed to extensively explore and find gastrinoma. The present study was designed to incorporate new state-of-the-art preoperative localization procedures as they became available. For example, in the mid-1980s, a number of studies reported increasing numbers of gastrinomas being found in extrapancreatic sites, primarily within the duodenum.[6,7,22,24,63,64] These gastrinomas were frequently small, missed by preoperative imaging studies, and could only be found by extensive search of the duodenum. Furthermore, one study in the mid-1980s reported that — in contrast to the original studies of Zollinger and Ellison, in which gastrinomas occurred at a rate of 20% in the duodenum and in a pancreatic distribution of 4:1:4 in the pancreatic head, body, and tail — 90% of gastrinomas were in the pancreatic head area, thus suggesting that many of the gastrinomas not being found in up to 50% of patients in some series might be in this area.[22] To address these issues, beginning in 1987 we added procedures (patients in group 2) to more intensively explore the duodenum, including intraoperative endoscopy with transillumination of the duodenum, the secretin angiogram with hepatic venous gastrin sampling to functionally localize gastrinomas,[52] and duodenotomy to those procedures that had been done before 1987 (Group 1). Regardless of the localizing test results in either group of patients, the current protocol required that a standardized surgical exploration be carried out in all patients with sporadic Zollinger–Ellison syndrome without evidence of liver metastases. Routine surgical exploration was carried out to find and remove gastrinomas for accurate staging and prognosis information, for control of the malignant potential of the tumor, and for potential cure of Zollinger–Ellison syndrome.

The results of the ability of surgery to cure a large number of patients with Zollinger–Ellison syndrome provide important information for physicians who are trying to manage these patients. First, the overall immediate disease-free rate as documented by a 3- to 6-month postoperative evaluation with normal serum gastrin levels, negative secretin and calcium provocative tests, and no evidence of tumor on imaging studies was 42 of 73 patients or 58% (Table 2). These results are better than every other modern prospective series except one recent study[29] involving small numbers of cases, which reported an immediate postoperative cure rate of 82%, in which patients were treated in similar fashion to patients in group 2 in the present study. The findings of the present study in combination with this other study[29] suggest that the short-term cure rate is significantly higher than that previously reported.[3,4,7,8,27,30] Second, the ability to find gastrinoma during the current study significantly improved as the study focused on the duodenum. Specifically, in the initial 6 years (1980 to 1986, group 1), gastrinomas were found in 64% of patients, whereas when additional procedures to localize duodenal gastrinomas were employed (group 2, 1987 to present), gastrinomas were found in 92% of patients. The increase was entirely due to localizing more duodenal gastrinomas, frequently of small size (< 6 mm). Because the preoperative imaging studies rarely localized these tumors, these results demonstrate that negative imaging studies, even when performed by the best experts available, will not reliably predict whether an experienced surgeon will find a tumor at surgery. Third, the increased ability to find and resect duodenal gastrinomas did not, as yet, result in a statistically significant improvement in cure rate (Table 2). However, there appears to be an upward trend (62% in group 2 *vs.* 52% in group 1, $p = 0.5$). Previous studies had suggested that extrapancreatic gastrinomas were more likely curable.[63–65] Our findings do not support this conclusion. In the present study, the ability to cure patients with duodenal gastrinomas was not greater than that for gastrinomas arising in other sites. In fact, the long-term disease-free rate for duodenal gastrinomas was lower. These results suggest that as increasingly more patients with duodenal gastrinomas are found that would have been missed without detailed duodenal exploration, the disease-free rate may increase, but not disproportionally to that seen in the patients with pancreatic gastrinomas. Fourth, the surgical procedure was done with a 11% morbidity rate and no deaths. Long-term morbidity rate was very low (1%). Fifth, the ability of gastrinoma excision to render disease-free patients with Zollinger–Ellison syndrome is maximum immediately after operation and decreases with length of follow-up. The long-term disease-free rate, in other words 5 years, is half the initial figure, or approximately 30% of all patients sustain long-term cure (Fig. 1, lower panel). This percentage is significantly higher than that suggested in older studies.[3,4,7,8,10,24,25,27,30] When this study was started, the reported long-term cure rate was less than 10%.[3,6-8,27,30] The current results in a large number of patients as well as data from other recent studies[26,29] suggest that the long-term cure rate may even be greater than 30%. The present study demonstrates that studies that suggest high cure rate with minimal follow-up[26,29,33,66] are likely to be significantly overestimating the true long-term cure rate. Furthermore, studies suggesting cure in which long-term repetitive gastrin provocative testing is not done are almost certainly overestimating the true long-term cure rate. In the present study of the 10 patients who developed evidence of recurrent Zollinger–Ellison syndrome, in six there was only functional data suggesting the recurrence (positive provocative testing with or without an elevated fasting gastrin concentrations), and in the remaining four, functional evidence as well as a gastrinoma on imaging studies. The results suggest that postoperatively all disease-free patients should have at least yearly evaluations with imaging studies and functional studies (basal acid output, fasting gastrin concentration, and gastrin provocative tests) to evaluate for continued cure.

The long-term disease-free rate in the present study also provides important information on which further treatment strategies can be based. Despite finding gastrinomas in 78% of all patients and in 92% of patients in group 2 in which specific additional procedures were added to localize duodenal gastrinomas, the disease-free rate fell off to 30% for all patients by 5 years. These results suggest it will be important to identify factors contributing to the development of recurrent disease and predicting which patients have a high risk of recurrence. The present results demonstrate that the location of the primary gastrinoma is one factor that is an important determinant of recurrence. In the present study the median disease-free interval was 5 times longer for patients cured after lymph node gastrinomas were removed (median, 60 months) and 7 times longer after resection of pancreatic gastrinomas (median, 84 months), than after resection of duodenal gastrinomas (median, 12 months). This finding is unexpected, and the basis for this finding is unclear. Numerous previous studies suggested that extrapancreatic gastrinomas are not only more likely to be curable than pancreatic tumors, but that duodenal gastrinomas have a lower malignant rate than do pancreatic gastrinomas.[63,65,67,68] This was proposed because pancreatic tumors were ectopic in nature, because the normal adult pancreas does not have G cells, whereas duodenal tumors were entopic, arising from G cells that are distributed in the adult duodenum.[67,68] In the present study, however, 55% of duodenal gastrinomas and 22% of pancreatic gastrinomas were associated with metastatic disease. These observations combined with the high recurrence rates with duodenal gastrinomas suggest that duodenal gastrinomas are more often malignant and are clearly not more likely to be curable, as proposed previously. It is likely in previous studies that small duodenal gastrinomas were frequently missed and that the detection of only lymph nodes led to an underestimation of the true malignant rate and curability. In the future, additional management steps directed at improving long-term cure rate in these patients will need to be identified.

Despite the malignant nature of gastrinoma as documented by recurrent disease and, in some patients, lymph node or liver metastases, antisecretory medications and surgery provide near perfect long-term survival of patients with sporadic Zollinger–Ellison syndrome who present without evidence of liver metastases (Fig. 2). These long-term survival results provide information that has a significant bearing on current management strategies. First, in the present study as well as in previous studies,[7,9,24,69] patients in whom no gastrinomas were found had survival rates of 80% to 100%, which was not significantly different from that for cured patients. The current results suggest that these missed tumors may most likely be small duodenal microgastrinomas. This excellent long-term prognosis contradicts recent studies[64,70,71] suggesting the use of Whipple pancreaticoduodenotomy after selective venous gastrin gradients that localize tumors to the pancreatic head area when no tumor can be located at surgery. At present, it is not clear that the morbidity rate and potential mortality rate of this procedure do not significantly outweigh its potential to increase cure and survival rate. Secondly, it may be argued, because the 5-year survival is >90% and is not significantly different in patients without a gastrinoma found than in patients with a gastrinoma resected but not cured, or in patients cured, that surgery is not indicated. There are, however, that there are a number of points that argue against this approach. It is unknown what percentage of the resected patients would have developed metastatic liver disease during follow-up if no surgery was done. We have observed other patients before this study who did not undergo surgical exploration who developed metastatic gastrinoma in the liver during follow-up. With the limited information available, the rate of such change is unknown and which patients will develop metastatic disease is unclear. Studies from carcinoid tumors that histologically resemble gastrinomas[11] demonstrate that the rate of developing metastatic disease is proportional to the size of the primary tumor. In patients with primary tumors < 1 cm in diameter, between 0% and 15% develop metastases, and in patients with >2-cm tumors, as many as 50% develop metastases.[19] Imaging studies rarely localize gastrinomas < 1 cm in diameter, 50% of gastrinomas 1 to 3 cm, and 70% > 3 cm[43-45]; therefore, with the use of radiographic imaging alone, gastrinomas < 3 cm are frequently missed and may only be found at surgery. If such patients had not undergone resection and developed metastatic disease, the prognosis would be generally poor, as shown in the present study for patients with metastatic disease. In contrast, the risk of laparotomy is low. Furthermore, in the patients who are disease free (up to 30%) the surgical procedure has long-term benefit. In these patients, antisecretory drugs can be stopped or markedly decreased, and the long-term potential risk of chronic hypergastrinemia or taking lifelong antisecretory agents can be avoided. In patients treated for up to 5 years with histamine H_2-receptor antagonists or omeprazole, there have been no drug-related side effects. All patients need to take these agents at least daily, however, and few patients have been maintained on these drugs longer than 5 years. Lastly, chronic hypergastrinemia can cause gastric carcinoid tumors in both humans and animals, some of which are malignant[17,72-74] and the long-term, lifetime risk of chronic hypergastrinemia has not been clearly defined. Therefore, for the 30% of patients disease free, long-term surgical removal may have significant long-term benefit.

In conclusion, this study of laparotomy and gastrinoma resection in patients with sporadic Zollinger–Ellison syndrome and no evidence of liver metastases suggests that tumors can be found in a higher proportion of patients than previously thought possible. In the last 37 consecutive patients, gastrinomas were found and excised in 34. This result was different from the findings in the initial 36 patients, and it became evident that the use of techniques to find duodenal gastrinomas accounted for the observed difference. The short-term disease-free rate was 58%. Careful long-term follow-up indicated that 50% of patients initially disease free developed recurrent disease by 5 years. Patients who developed evidence of recurrent disease by radiographic imaging studies still were able to have all recurrent tumor removed for control. Surgery was performed with acceptable morbidity and mortality rates. This strategy of medical management of gastric acid hypersecretion and surgical resection of gastrinoma resulted in no deaths from Zollinger–Ellison syndrome or treatment during the current follow-up period (>4 years). This study suggests that patients with Zollinger–Ellison syndrome can be effectively and safely managed by antisecretory medications to control gastric acid hypersecretion and surgery to control malignant potential of tumor in nearly all patients and to cure 30% of patients.

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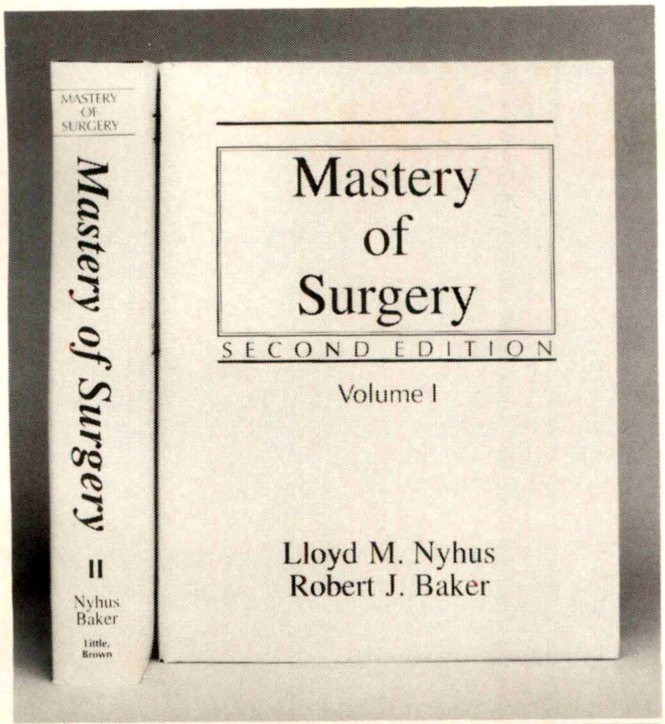

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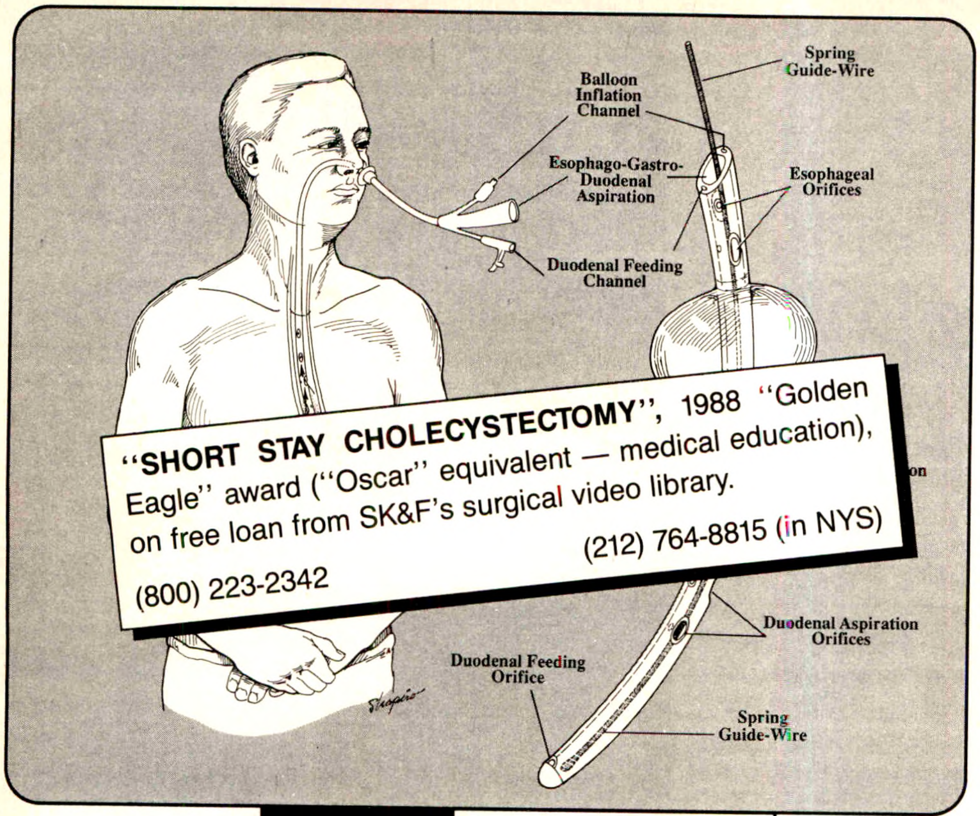

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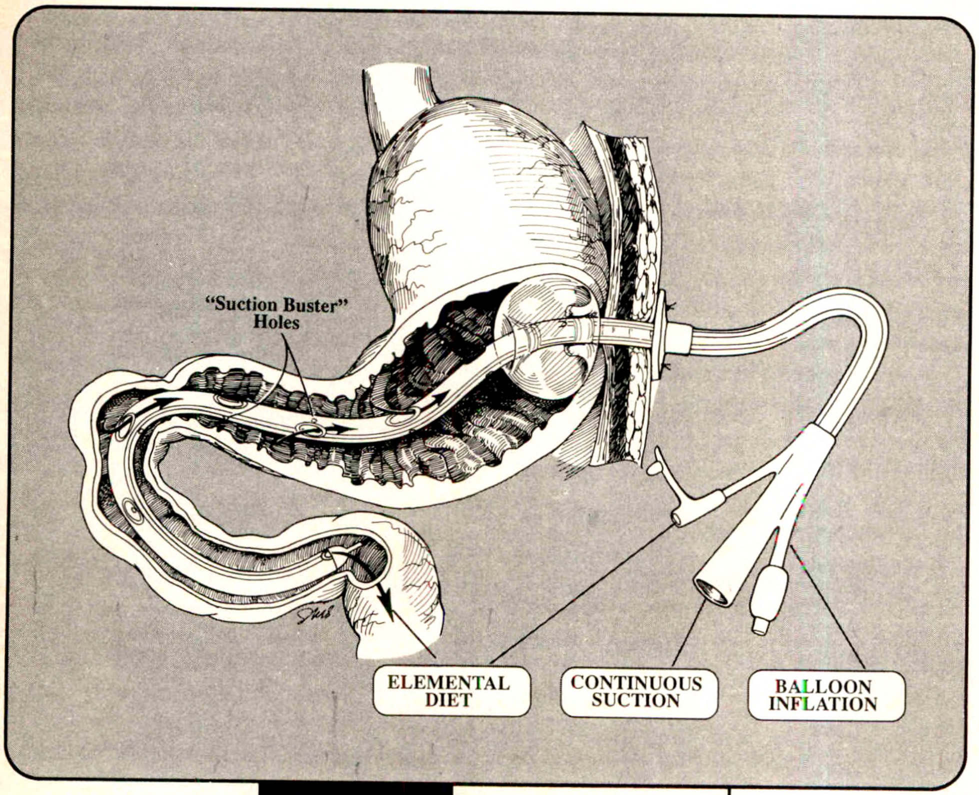

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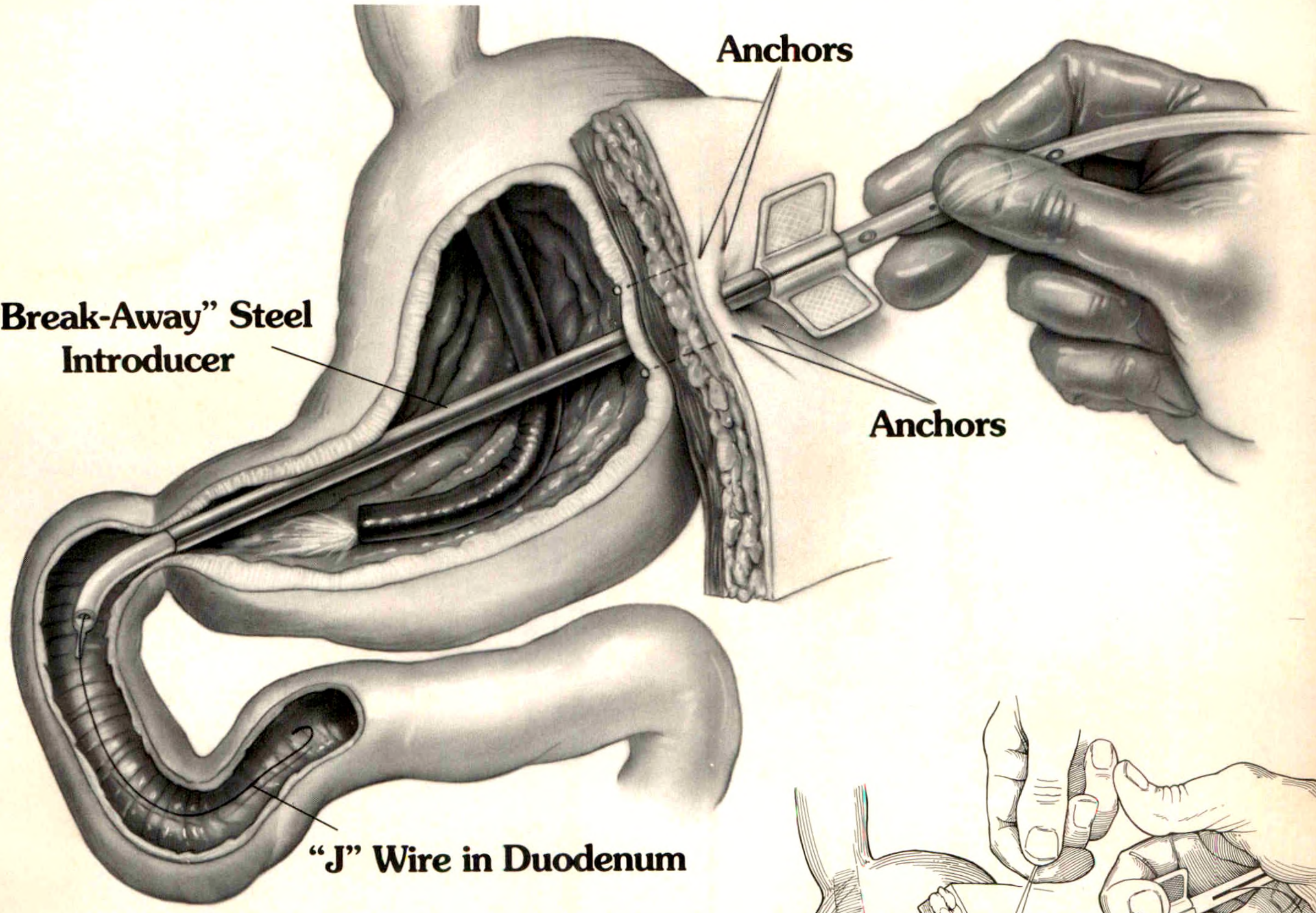

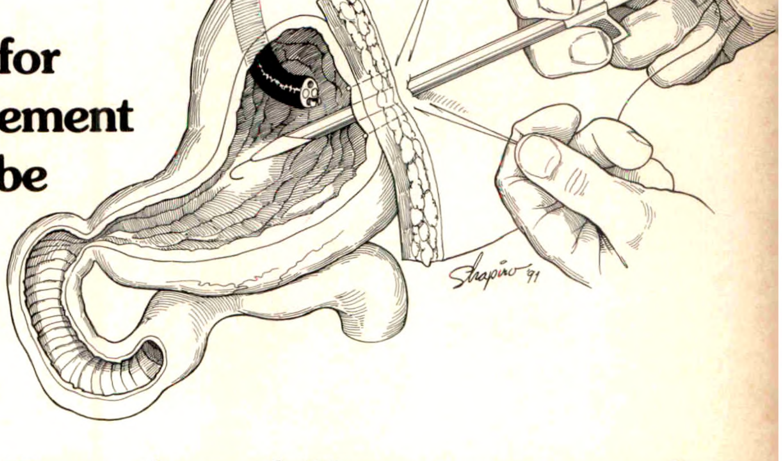

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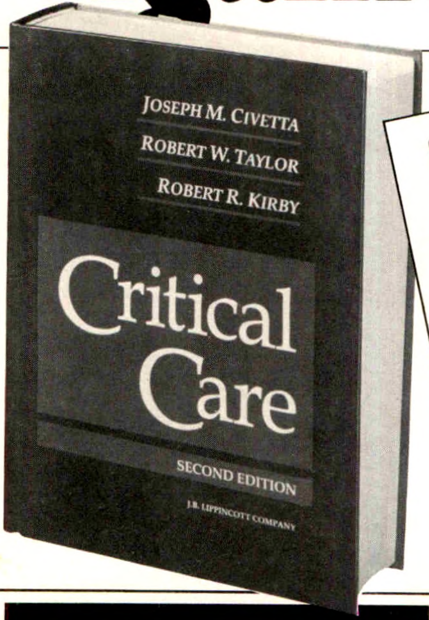

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Gallbladder Sludge and Stone Formation in Relation to Contractile Function After Gastrectomy

A Prospective Study

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In a prospective trial to determine whether gastric surgery induces gallbladder sludge and stone formation, 48 patients with gastric cancer were ultrasonographically examined with simultaneous observation on changes in gallbladder contractile function before and serially for 5 years after gastrectomy. Gallbladder sludge formation was induced with a high frequency of 42% 1 month after gastrectomy, with corresponding significant lowering of gallbladder contractile function. Most of gallbladder sludges, however, disappeared within 12 months in relation to the gradual recovery of gallbladder contractile function. Conversely, gallstone developed in nine patients (18.8%), mostly more than 6 months after gastrectomy. Interestingly, gallstone formation was induced in seven patients who were sludge negative. An evolvement of gallbladder sludge into stone was observed in only two patients, who were, however, treated with intravenous hyperalimentation. This study first provides evidence for the relationship between gastrectomy and a considerably high frequency of incidence of gallbladder sludge and stone in relation to changes in gallbladder kinetics after gastrectomy.

SINCE MAJOOR AND SUREN first drew attention to the possible association of gallstones with gastric surgery, an increased incidence of gallstones has been widely reported in patients with gastrectomy.[2-9] There has been, however, very little information about the pathophysiologic mechanism for the occurrence of gallbladder disease after gastric surgery. Most of the studies on gallstone disease after gastrectomy have been retrospective.[1-9] No report has been available to carry out a prospective study on pathophysiology of gallbladder in relation to changes of gallbladder contractile function after gastrectomy.

In this study, we performed a prospective serial ultrasonographic study on changes of gallbladder volume and contractile function with special reference to sludge[10-13] formation and cholelithiasis in gastric cancer patients who have undergone gastrectomy.

Patients and Methods

Adult patients with gastric cancer who were about to undergo gastric surgery were studied. Conditions necessary for the present prospective study include absence of gallbladder disease, as assessed by both preoperative ultrasonographic study and careful examination of the gallbladder at the time of surgery, no pyloric stenosis, no laboratory alterations in liver function test, and no injection of insulin, opiates, or anticholinergic drugs.

A total of 48 patients (33 men, 15 women; mean age of 56 years) were examined. All of them were patients with relatively early stage of gastric cancer.[14,15] Curative resection was performed on all of the patients based on the general rules for gastric cancer in Japan.[15] The surgical procedures carried out are as follows; subtotal gastrectomy with Billroth I anastomosis (30 patients), with Billroth II anastomosis (3 patients), total gastrectomy with interposition reconstruction (6 patients), and with Roux-en-Y reconstruction (9 patients).

Postoperative course was uneventful without any sign of cholecystitis in these patients, except in three cases with postoperative complications (leakage, pancreatitis, and passage disturbance), who were treated with intravenous hyperalimentation with postoperative fasting for 33 to 34 days. The period of postoperative fasting was about 3 to 5 days after subtotal gastrectomy (30 patients) and 8 to 13 days after total gastrectomy (15 patients).

By comparison, seven patients with colon cancer (five men, two women; mean age of 54) also were examined.

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The operative procedures performed were partial colonic resection (five patients) and right hemicolectomy (two patients). The period of postoperative fasting for these patients was 3 to 5 days.

Ultrasonographic Study on Gallbladder

Ultrasonographic examination was prospectively carried out before (48 patients) and serially 1 week (36 patients), 2 weeks (38 patients), 1 month (40 patients), 3 months (29 patients), 6 months (31 patients), 12 months (44 patients), about 24 months (13 patients), and about 60 months (9 patients) after operation. For patients with colon cancer, ultrasonographic examination was carried out before (7 patients) and 1 week (5 patients), 2 weeks (6 patients), 1 month (7 patients), 3 months (6 patients), 6 months (7 patients), and 12 months (6 patients) after colonic surgery. Ultrasonographic examination was begun early in the morning (about 8:30 A.M.) after an overnight fast. Sonograms of the gallbladder were obtained by a real time ultrasound unit (Aloka, Tokyo, Japan) with a 3.5-MHz phased-array transducer.

Examination on Sludge and Stone Formation

In this study, we classified gallbladder sludges observed into four types (scattered type [S], tumefactive type [T], layering type [L], and precipitated type [P]) (Fig. 1) and gallstones into two types (strong echo without acoustic shadow [SE] and strong echo with acoustic shadow [ST]).

Observation on Changes in the Resting Gallbladder Area

Changes in the resting gallbladder area were observed before (48 patients) and serially 1 week (36 patients), 2 weeks (38 patients), 1 month (40 patients), 3 months (29 patients), 6 months (31 patients), 12 months (44 patients), and 60 months (9 patients) after gastrectomy. For patients with colon cancer, the same study was performed before (7 patients) and 1 week (5 patients), 2 weeks (6 patients), 1 month (7 patients), 3 months (6 patients), 6 months (7 patients), and 12 months (6 patients) after colonic surgery.

Study on Changes in Gallbladder Contractile Function

Prospective studies on changes of gallbladder contractile function were performed on 35 patients, employing cerulein as an exogenous stimulation of cholecystokinin (CCK).[16–19] Cerulein (0.2 μg/kg) was injected intramuscularly to each patient before (35 patients) and 1 month (27 patients), 3 months (25 patients), 6 months (26 patients), 12 months (30 patients), and 60 months (9 patients) after gastrectomy. Cerulein (0.2 μg/kg) also was injected into patients with colon cancer before (7 patients) and 1 month (7 patients), 3 months (5 patients), 6 months (6 patients), and 12 months (6 patients) after colonic sur-

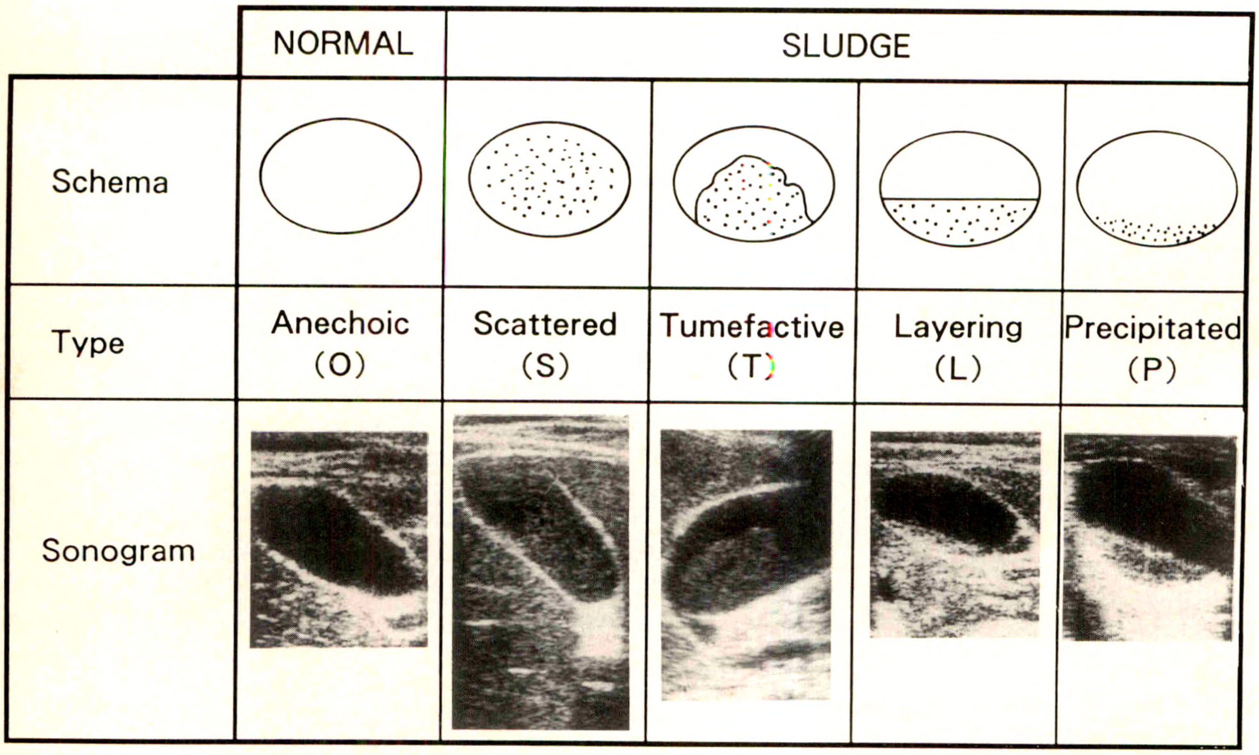

FIG. 1. Ultrasonographic classification of gallbladder sludge observed after gastrectomy.

gery. In each study, changes of gallbladder areas in response to cerulein were observed for 120 minutes at 10-minute intervals for the first 60 minutes and at 20-minute intervals thereafter. Gallbladder areas were measured by planimeter from photographs and expressed as percentages of the original resting areas. Each value was expressed as mean ± standard error of the mean (SEM). Student's t test was used to analyze the data obtained from the study on gallbladder contractile function for statistical difference. Values of $p < 0.05$ were considered significant. In-

FIG. 2. Serial changes in types of gallbladder sludge and stone in each of 48 patients with gastric cancer after gastrectomy.

No.	Case	Age	Sex	Reconstruction Method*	Post-operative fasting days	Before Operation	Post-1W	Post-2W	Post-1M	Post-3M	Post-6M	Post-12M	Over 12M	Post-5Y
1	T.M.	61	M	BI	4	○	○	○	○	○	$\boxed{SE}$	○	→··········→	○ (54)
2	M.T.	51	F	BI	4	○	○	○	○	○	○	$\boxed{ST}$	○ (24)***	
3	M.Y.	26	F	BI	4	○	···	○	○	···	···	$\boxed{SE}$	$\boxed{SE}$ (20)	
4	K.A.	72	M	BI	5	○	···	···	···	···	···	$\boxed{ST}$		
5	M.Y.	39	M	BI	33**	○	S	S	S	$\boxed{ST}$	$\boxed{ST}$	$\boxed{ST}$	$\boxed{ST}$ (28)	
6	H.Y.	32	M	BI	34**	○	○	L	L	P	$\boxed{SE}$	$\boxed{SE}$		
7	M.K.	53	M	BI	4	○	···	···	S	L	P	P	○ (24)	
8	T.S.	35	F	BI	3	○	L	P	P	P	P	○		
9	S.Y.	71	M	BI	6	○	S	L	P	P	P	○		
10	H.I.	39	F	BI	33**	○	···	···	L	P	P	○	→··········→	○ (59)
11	K.K.	41	M	BI	4	○	T	L	P	P	○	○	○ (20)	
12	K.M.	43	M	BI	3	○	S	L	P	P	○	○	○ (16)	
13	S.T.	73	F	BI	6	○	S	S	L	···	○			
14	R.T.	56	M	BI	4	○	S	S	S	○	○	○	○ (25)	$\boxed{SE}$ (62)
15	K.K.	74	M	BI	4	○	L	P	○	···	○	○		
16	S.Y.	48	M	BI	3	○	S	S	○	···	○	○	→··········→	○ (54)
17	S.O.	59	M	BI	5	○	○	○	○	○	○	○	○ (24)	○ (57)
18	J.Y.	44	M	BI	4	○	○	○	○	○	○	○		
19	M.N.	51	M	BI	4	○	···	○	○	○	○	○		
20	F.Y.	68	F	BI	4	○	○	○	○	○				
21	K.A.	48	M	BI	3	○	○	○	○	···	···	○		
22	K.T.	77	M	BI	4	○	○	○	○	···	···	○		
23	Y.U.	66	M	BI	3	○	○	○	○	···	···	○		
24	H.K.	57	M	BI	3	○	○	···	○	···	···	○		
25	A.K.	48	F	BI	3	○	○	○	···	···	···	○		
26	S.T.	49	M	BI	4	○	···	···	···	···	○	○	○ (24)	→
27	K.N.	70	M	BI	8	○	···	···	···	···	···	○		
28	K.H.	42	M	BI	4	○	···	···	···	···	···	○		
29	W.Y.	57	M	BI	4	○	···	···	···	···	···	○		
30	T.Y.	39	M	BI	3	○	···	···	···	···	···	○		
31	T.O.	73	M	BII	4	○	○	○	○	○	○	○		
32	T.Y.	58	M	BII	4	○	○	○	○	···	○	○		
33	S.N.	81	F	BII	5	○	○	○	···	···	···	○		
34	K.N.	62	M	IP	9	○	○	○	○	○	···	$\boxed{ST}$	$\boxed{ST}$ (19)	
35	H.M.	60	F	IP	13	○	S	P	P	○				
36	T.T.	61	F	IP	12	○	○	○	○	○	○	○		
37	T.S.	80	M	IP	9	○	○	○	○	○	○	○		
38	T.I.	54	F	IP	8	○	○	○	○	○	···	○		
39	C.F.	39	M	IP	8	○	○	○	○	···	○	○		
40	C.H.	73	M	RY	7	○	S	S	P	P	P	P		
41	Y.T.	66	M	RY	8	○	S	S	L	P	○	L	○ (21)	
42	A.K.	53	F	RY	10	○	S	T	L	L	L	○	○ (14)	$\boxed{ST}$ (60)
43	K.Y.	53	F	RY	6	○	···	···	L	P	○	○	○ (21)	
44	F.O.	45	F	RY	13	○	T	S	P	○	○	○	→··········→	○ (63)
45	K.K.	65	M	RY	18	○	S	L	P	○	○			
46	M.T.	49	F	RY	10	○	○	○	○	○	○	○	→··········→	○ (55)
47	H.K.	49	M	RY	8	○	○	○	○	○	○	○	→··········→	○ (53)
48	I.K.	57	M	RY	7	○	···	○	○	···	···	○		

* BI ; Subtotal Gastrectomy With Billroth I Reconstruction
BII ; Subtotal Gastrectomy With Billroth II Reconstruction
IP ; Total Gastrectomy With Interposition Reconstruction
RY ; Total Gastrectomy With Roux-enY Reconstruction
** With Intravenous Hyperalimentation
*** ( ) ; Post-Operative Months

(W : Weeks
M : Months
Y : Years)

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TABLE 1. *Frequency of Sludge and Stone Formation in the Gallbladder After Gastrectomy*

	Post-1 wk (n = 36)	Post-2 wk (n = 38)	Post-1 mo (n = 40)	Post-3 mo (n = 29)	Post-6 mo (n = 31)	Post-12 mo (n = 44)	Post-60 mo (n = 9)
Sludge	42% (n = 15)	42% (n = 16)	43% (n = 17)	38% (n = 11)	19% (n = 6)	7% (n = 3)	0% (n = 0)
Stone	0% (n = 0)	0% (n = 0)	0% (n = 1)	3% (n = 1)	10% (n = 3)	14% (n = 6)	22% (n = 2)

formed consent was obtained from each patient. All investigations were carried out in accordance with the World Medical Association Declaration of Helsinki, adopted in 1964 and amended in 1975, 1983, and 1989.

Results

Sludge Formation in the Gallbladder

Gallbladder sludge formation was frequently induced in the very early postoperative period after gastrectomy (Fig. 2, Table 1). The frequencies of gallbladder sludge formation 1 month after gastrectomy were 100% in subtotal gastrectomized patients with intravenous hyperalimentation (3/3), 47% in patients with total gastrectomy (7/15), and 38% in patients with subtotal gastrectomy (7/22) (Fig. 2). Sludge positivity thereafter was gradually decreased to 19% at 6 months and prominently decreased to only 7% at 12 months (Fig. 2, Table 2). Furthermore, two of the 3 patients who were sludge positive at 12 months after gastrectomy were later found to be sludge negative at 21 months (case 41, Fig. 2) and at 24 months (case 7, Fig. 2), respectively.

Regarding the type of gallbladder sludges, the most frequent pattern of changes during the follow-up course is as follows; scattered type (S) → layering type (L) → precipitated type (P) → anechoic type (O) (Fig. 1, Fig. 2, Table 2). Patients with colon cancer showed no development of sludges at any observation period after colonic surgery.

Stone Formation in the Gallbladder

Gallstone formation was observed in nine of 48 patients with gastrectomy (18.8%) during the follow-up period of approximately 5 years. In four cases with development of gallstone (cases 1, 2, 3, and 34), no presence of sludge has been found until the formation of the stone (Fig. 2). In cases 14 and 42, although gallbladder sludge had been induced once after gastrectomy, sludge had completely disappeared within 3 months and 12 months, respectively. Gallstone formation occurred, however, 5 years after gastrectomy. In cases 1 and 2, spontaneous disappearance of gallstone was observed at 12 months and 24 months, respectively (Fig. 2). In two gastrectomized patients with intravenous hyperalimentation, changes of gallbladder sludge to the strong echo were demonstrated at 3 months (case 5) and 6 months (case 6), respectively, indicating the direct evolvement of the sludge into the stone (Fig. 3). The echotomograms of gallstones induced in another seven cases after gastrectomy are represented also in Figure 4. Of 9 cases with gallstone, a single stone was found in six cases, whereas multiple stones were found in three cases, smaller than 9 mm in all cases. All of the patients with either gallbladder sludge formation or gallstone formation were asymptomatic, and no alterations of the gallbladder wall suggestive of cholecystitis were seen.

One patient (case 4) required cholecystectomy on the 13th month after gastrectomy because of multiple stones. Cholecystectomy showed that there were five pigment stones 3 to 9 mm in diameter in the gallbladder of this

TABLE 2. *Serial Changes in Types of Gallbladder Sludge and Stone After Gastrectomy*

	Post-1 wk	Post-2 wk	Post-1 mo	Post-3 mo	Post-6 mo	Post-12 mo	Post-60 mo
Sludge							
S	11	7	3	0	0	0	0
T	2	1	0	0	0	0	0
L	2	5	6	2	1	1	0
P	0	3	8	9	5	2	0
Stone							
SE	—	—	—	—	2	2	1
ST	—	—	—	1	1	4	1

Each value represents the number of patients with either ultrasonographic sludge or strong echo.

S, scattered type; T, tumefactive type; L, layering type; P, precipitated type; SE, strong echo without acoustic shadow; ST, strong echo with acoustic shadow.

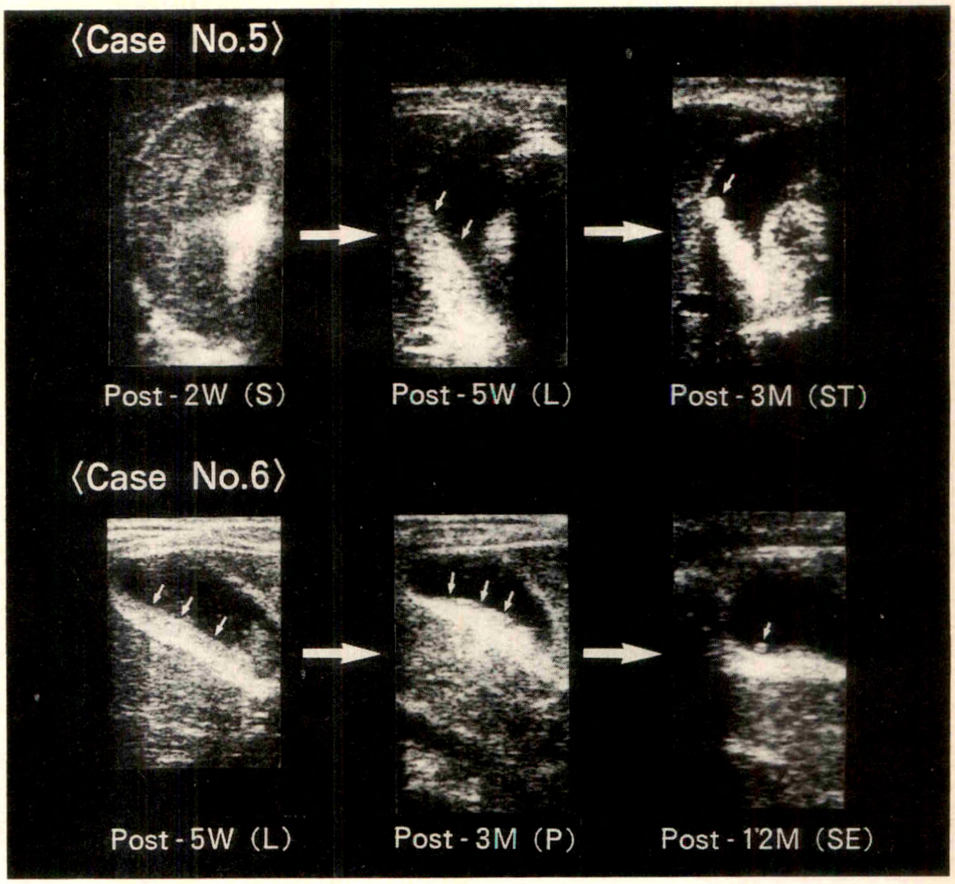

FIG. 3. Ultrasonographic observation on time course of evolvement of gallbladder sludge into the stone in gastrectomized patients with intravenous hyperalimentation. SE, strong echo without acoustic shadow; ST, strong echo with acoustic shadow; W, week; M, month.

patient. No formation of gallstone has been observed in patients with colonic surgery.

Changes in the Resting Gallbladder Area

The resting gallbladder area (Fig. 5) was significantly enlarged to 154% ± 9% of the original area (pregastrectomy) 1 week after gastrectomy, remaining significantly enlarged up to 12 months after gastrectomy. This dilatation of gallbladder, however, returned to pregastrectomy levels 60 months after gastrectomy. No significant changes in the resting gallbladder area were induced by colonic surgery.

Changes in Gallbladder Contractile Function

Gallbladder contractile function was significantly suppressed 1 month after gastrectomy, showing the decreased maximal gallbladder contraction rate of 55.2% ± 5.8% at 30 minutes (calculated as the percentage of that observed before gastrectomy) after cerulein stimulation. Although this significant suppression of gallbladder contractile function has lasted for 6 months after gastrectomy, the contractile function showed a gradual recovery thereafter, attaining the maximal gallbladder contraction rate of 91.7% ± 7.4% at 12 months (Fig. 6). Gallbladder contractile function in patients with colon cancer showed no significant changes at any observation period after colonic surgery compared with that before operation.

Discussion

The present prospective study first provides evidence for the relationship between gastrectomy and a considerably high frequency of incidence of gallbladder sludge and stone, with simultaneous serial observation on changes in gallbladder contractile function. Since the widespread use of the ultrasonography in the assessment of the biliary tract, the presence of sludge in the gallbladder has been observed frequently.[10–12] The relationship between prolonged total parenteral nutrition and gallbladder sludge formation has been reported, suggesting that bowel rest and bile stasis during parenteral nutrition lead to production of sludge.[13] Bolondi et al[14] have observed gallbladder sludge formation during prolonged fasting after gastrointestinal surgery, indicating that the formation of gallbladder sludge was induced in 15% of patients with postoperative fasting for 7 days and in 32% of patients with postoperative fasting for 10 days, respectively, after gastrointestinal surgery.

The present serial and prospective study with postoperative fasting for 3 to 5 days for subtotal gastrectomy

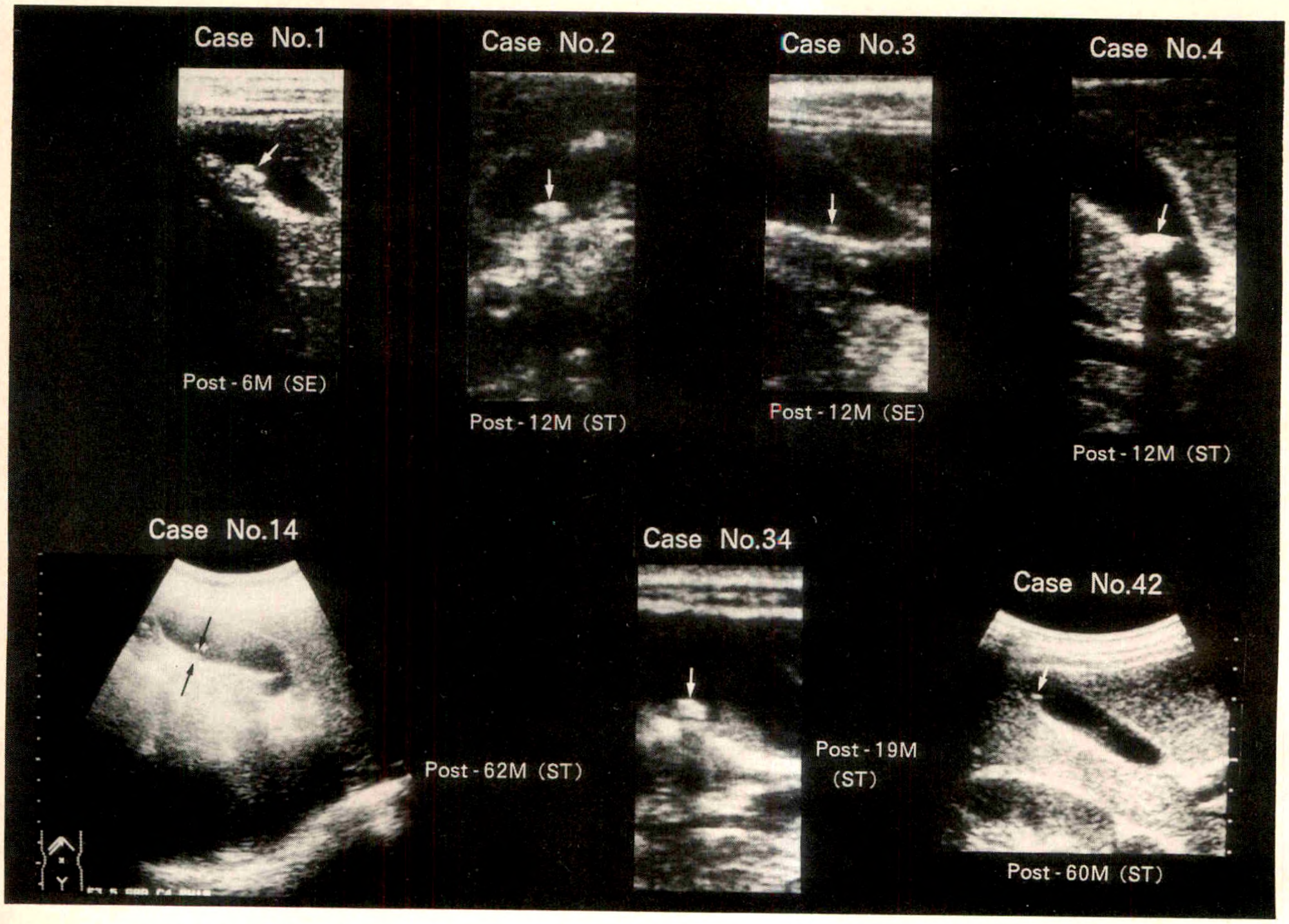

FIG. 4. Ultrasonographic observation of gallstones induced after gastrectomy. SE, strong echo without acoustic shadow; ST, strong echo with acoustic shadow; W, week; M, month.

and for 8 to 13 days for total gastrectomy demonstrated a high frequency of gallbladder sludge formation of 38% in patients with subtotal gastrectomy and of 47% in patients with total gastrectomy, respectively, with corresponding significant lowering of the gallbladder contractile function (Fig. 6).

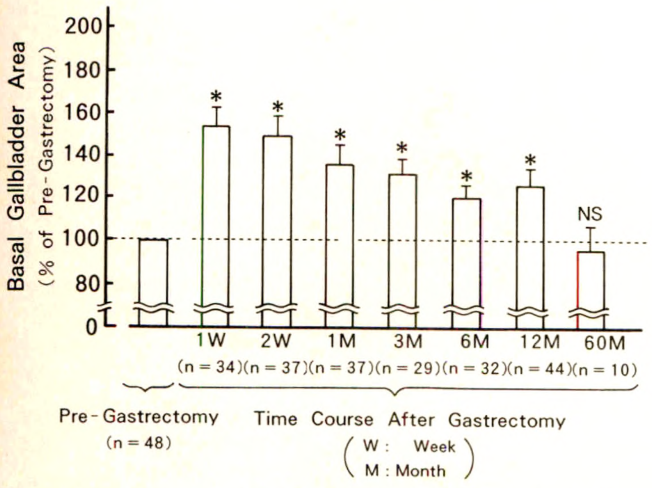

FIG. 5. Serial changes in the basal (resting) gallbladder area after gastrectomy. *$p < 0.05$.

The time course of the gradual disappearance of the gallbladder sludge (Fig. 2, Table 1) was closely related to that of the gradual recovery of gallbladder contractile function (Fig. 6), suggesting that the gradual disappearance of gallbladder sludges could be, at least partly, attributed to the corresponding recovery of the gallbladder contractile function after gastrectomy.

The present study also demonstrated that gallbladder sludges observed after gastrectomy showed an unique pattern of changes during the follow-up course: scattered type → layering type → precipitated type (Fig. 1, Fig. 2, Table 2). Most of these gallbladder sludges, however, disappeared within 12 months after gastrectomy, except two cases with intravenous hyperalimentation in which evolvement of gallbladder sludge into the stone was observed (Fig. 3). It has been clarified that patients who receive long-term total parenteral nutrition are at increased risk for the development of cholelithiasis.[13,20] Messing et al.[13] observed the prevalence of gallbladder sludge for-

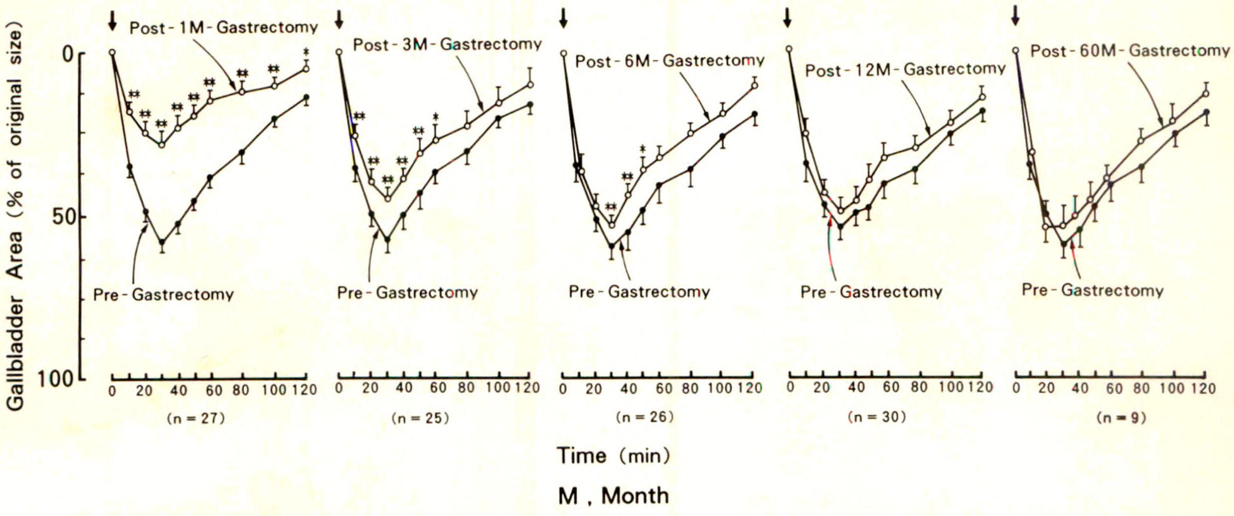

FIG. 6. Time course of changes in the gallbladder contractile function in response to cerulein (0.2 μg/kg intramuscularly) after gastrectomy. M, month. *p < 0.05; **p < 0.01.

mation during total parenteral nutrition and further found that gallstone formation was induced in sludge-forming patients, but not in patients who were sludge negative. Their observation is consistent with above-mentioned two gastrectomized cases with intravenous hyperalimentation in our study (Fig. 3). On the contrary, all of the other patients who developed gallbladder sludges in our study did not show any evolvement of gallbladder sludge into gallstone, but showed complete disappearance of gallbladder sludges during the follow-up course after gastrectomy. Thus, the present study first demonstrated that development of gallstone was induced mostly in patients who had shown no formation of gallbladder sludges and slightly in patients who were sludge negative, but had been sludge positive before, suggesting that development of gallstone observed after gastrectomy has very little to do with formation of gallbladder sludges. This phenomenon leads us to presume that the pathophysiology of gallstone formation after gastrectomy could be, to some extent, different from that observed during total parenteral nutrition, which is capable of evolving gallbladder sludge into gallstone.[13]

Observations on the function as well as on the volume of the gallbladder after gastric surgery have been controversial.[2,21-24] The present study first performed consecutive and prospective observation on these subjects. A possible explanation for a dilatation of the gallbladder after gastrectomy could be sectioning of the hepatic branch of the vagus nerve,[2,7,8,9,21,22] which plays an important role in regulating the tonicity of the gallbladder.[25] In our study, to perform curative resection, lymph nodes of both the first and second group[15,16] were removed so that the anterior hepatic branch of the vagus nerve was inevitably dissected in each patient. No dilatation of the gallbladder was observed during the follow-up course after colonic surgery, leading us to realize the importance of the hepatic branch of the vagus nerve for retaining the tonicity of the gallbladder.

With regard to the humoral factor that affects gallbladder contractile function, CCK is supposed to play a physiologically important role in the modulation of gallbladder contraction.[17-19] We cannot deny a possibility that significant dilatation of the gallbladder, which was observed even 12 months after gastrectomy, might cause bile stasis, leading to the formation of gallstones. It may be, however, more likely that changes in the release of CCK, followed by changes in the gallbladder kinetics, in response to the physiologic endogenous stimulation, could be deeply involved in the incidence of gallstones after gastrectomy.[1-9,21] In 1958, Cox et al.[2] speculated that an excessive amount of CCK is liberated after gastrectomy. This hypothesis was confirmed later by several studies[19,26] that demonstrated a significantly augmented plasma CCK response to oral ingestion of fat after gastrectomy. An augmented plasma CCK response to the ingestion of a fatty meal[19,26] could be at least partly due to the rapid gastric emptying after gastretomy.[27] Masclee et al.[28] have investigated the intestinal phase of CCK release and gallbladder emptying in patients with partial gastrectomy by precluding the effect of gastric emptying and the effect of cephalic and gastric phases of gallbladder contraction, in which CCK is not involved,[29] finding the delayed plasma CCK and gallbladder responses to intestinal fat. The impaired vagal-cholinergic stimulation of pancreatic enzyme after gastrectomy may result in reduced fat digestion, followed by subsequent and delayed plasma CCK and gallbladder responses to intestinal fat. We have observed that CCK showed a rapid and greater response to oral fatty meal 1 month after gastrectomy, but refilling of the gallbladder was induced much earlier, with corresponding earlier reduction of plasma CCK, without showing any consistent gallbladder contraction phase before gastrectomy.[19] We also have observed similar phenomena 12 months after gastrectomy (unpublished observation). The incidence of gallstones after gastrectomy may be due at least partly to the changes of endogenously released CCK, followed by the changes in gallbladder kinetics, leading to the bile stasis, which could result in eventual gallstone formation, especially when accompanied by the retrograde biliary infection or reduction of the total bile acid pool.[30] The pathophysiologic mechanism for the incidence of gallstones after gastrectomy needs further investigation.

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Congenital Choledochal Dilatation With Emphasis on Pathophysiology of the Biliary Tract

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Of 37 patients with congenital choledochal dilatation, aged 8 days to 12 years, who had undergone excision with Roux-en-Y hepaticojejunostomy, 26 patients could be analyzed for morphologic abnormalities and pathophysiology of the biliary tract. Of the 26 patients with congenital choledochal dilatation, 25 (96.2%) had an abnormal choledochopancreaticoductal junction. Of the 12 patients with cystic-type choledochal dilatation, 10 had the C-P type of abnormal choledochopancreaticoductal junction, and of the 13 patients with fusiform-type choledochal dilatation, nine had the P-C type. The amylase levels in the choledochal cyst and the gallbladder were elevated regardless of the form of choledochal dilatation. An adenocarcinoma in a cystic choledochal dilatation was found in one child. Therefore, longstanding inflammation of the biliary tract caused by the reflux of pancreatic juice might be one of the factors in carcinogenesis in the biliary tract. This free reflux of pancreatic juice was demonstrated not only by amylase levels in the biliary tract but also by intraoperative biliary manometry. This reflux might be explained by the lack of sphincter function at the junction of the common bile and pancreatic ducts.

ADVANCES IN ENDOSCOPIC retrograde cholangiography (ERCP) in infants have provided further elucidation of the relationship between congenital choledochal dilatation and abnormalities of the choledochopancreaticoductal junction. However, little is known about the pathophysiology of the biliary tract in patients with congenital choledochal dilatation.

This paper describes morphologic abnormalities and the pathophysiology of the biliary tracts of the 37 patients with congenital choledochal dilatation. In addition, the pathophysiology, which might lead to malignant degeneration in the biliary tract, is discussed.

Clinical Data

Thirty-seven patients with congenital choledochal dilatation were treated at the Division of Surgery, Children's Research Hospital, Kyoto Prefectural University of Medicine from 1978 to 1990. The mean age of the nine male patients was 2 years 6 months (range, 8 days to 5 years). The mean age of the 28 female patients was 3 years 10 months (range, 1 month to 12 years) (Table 1). During the follow-up period of 1 to 13 years, 36 patients have been doing well. However, one patient—a 12-year-old girl[1]—died of adenocarcinoma arising from the distal part of the cyst in the infrapancreatic region 2 years after operation.

Excision of choledochal cyst followed by Roux-en-Y hepaticojejunostomy was performed in all 37 patients. The cyst was proximally transected at the hepatic hilum, and distally resected at the level of the infrapancreatic region.

The biliary tract was examined by preoperative ERCP or operative cholangiography in all 37 patients. Union of the common bile duct and the main pancreatic duct could be clearly demonstrated in 26 patients, 16 by ERCP, 3 by operative cholangiography, and 7 by both procedures. The findings were classified into three types of abnormal choledochopancreaticoductal junction: (1) C-P type, the bile duct joins the pancreatic duct, which is the major duct (Fig. 1); (2) P-C type, the pancreatic duct joins the bile duct, which is the major duct (Fig. 2); (3) miscellaneous type, the connection between the common bile duct and the pancreatic duct is too complex to be categorized as either C-P or P-C type.

Biliary manometry could be performed in the most recently treated 11 of the 37 patients. Pressure recordings were obtained with a polyvinyl catheter with an internal diameter of 0.8 mm and an outer diameter of 1.0 mm. The probe was filled with sterile solution, and perfusion took place at a constant rate of 30 mL/hour. This appa-

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TABLE 1. *Patients With Congenital Choledochal Dilatation*

Sex	No. of Patients	Mean Age (range)
M	9	2 yr, 6 mo (8 day–5 yr)
F	28	3 yr, 10 mo (1 mo–12 yr)
Total	37	3 yr, 6 mo (8 day–12 yr)

ratus was connected to a transducer (Gould Inc., P231D, Oxnard, CA), and the pressures were recorded with a Nippon-Sanei thermal pen recorder. Zero pressure, used throughout this study, was determined by recording atmospheric pressure at the distal end of the common bile duct. To obtain pressure recordings from the biliary duct system, the probe was inserted into the sphincter of Oddi through the distal end of the common bile duct and the abnormal choledochopancreaticoductal junction. The probe was withdrawn from the duodenum to to the biliary tract at a constant speed of 0.8 mm/second. The pressure profile of the biliary tract was recorded in centimeters as the probe was withdrawn. Tetragastrin (4 r/kg) was injected intravenously, and manometric studies of the biliary tract were performed before and 3 minutes after the injection.

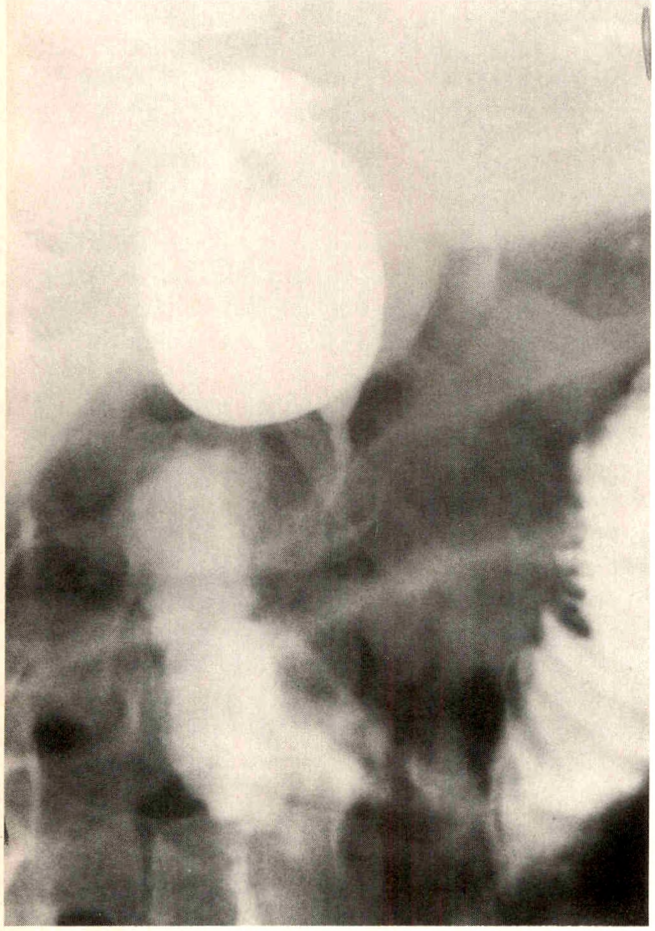

FIG. 1. C-P type of abnormal choledochopancreaticoductal junction. The bile duct joins the pancreatic duct.

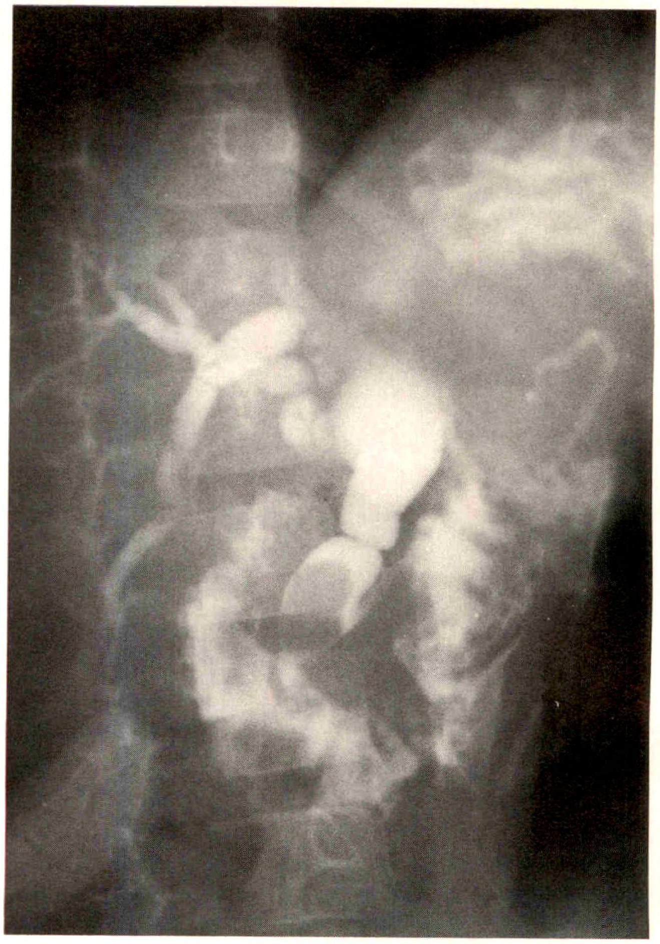

FIG. 2. P-C type of abnormal choledochopancreaticoductal junction. The pancreatic duct joins the bile duct.

Informed consent was obtained from the parents before performing intraoperative biliary manometry.

Results

Types of Abnormal Choledochopancreaticoductal Junction in Relation to Forms of Choledochal Dilatation

Twenty-six patients with congenital choledochal dilatation could be analyzed by preoperative ERCP or by operative cholangiography whether they had an abnormal choledochopancreaticoductal junction or not (Table 2). An abnormal choledochopancreaticoductal junction was noted in 25 of the 26 patients (96.2%) with congenital choledochal dilatation. The remaining patient (3.8%), with a fusiform choledochal dilatation, had no abnormal choledochopancreaticoductal junction.

Of the 12 patients with cystic dilatation, 10 had the C-P type, 1 had the P-C type, and 1 had the miscellaneous

TABLE 2. *Forms of Choledochal Dilatation and Abnormal Choledochopancreaticoductal Junction*

Form of Choledochal Dilatation	No. of Patients	Abnormal Choledochopancreaticoductal Junction			
		C-P type	P-C type	Miscellaneous	Absent
Cystic	12	10	1	1	—
Fusiform	13	2	9	1	1
Multicystic	1	—	—	1	—
Total	26	12	10	3	1

TABLE 3. *Forms of Choledochal Dilatation and Amylase Levels in Cyst and Gallbladder*

Form of Choledochal Dilatation	No. of Patients	Amylase Levels	
		Cyst	Gallbladder
Cystic	22	59,969 ± 14,311	80,065 ± 18,724
Fusiform	13	42,160 ± 9091*	91,284 ± 24,238*
Multicystic	2	NE	200,010.0

Mean ± SE.
* $0.05 < p < 0.1$
NE, not examined.

type of junction. Of the 13 patients with fusiform dilatation, 9 had the P-C type, 2 had the C-P type, and 1 had the miscellaneous type of junction, and 1 had a normal junction. One patient had a multicystic type of dilatation and the miscellaneous type of abnormal choledochopancreaticoductal junction.

Amylase Levels in Choledochal Cyst and Gallbladder

In 22 patients with cystic dilatation the mean amylase levels in the choledochal cyst and the gallbladder were 59,969 ± 14,311 Somogyi Units and 80,065 ± 18,724 Somogyi Units, respectively (Table 3). In 13 patients with fusiform dilatation, the mean amylase level in the gallbladder (91,284 ± 24,238 Somogyi Units) was higher ($0.05 < p < 0.1$) than that in the choledochal cyst (42,160 ± 9,091 Somogyi Units). In two patients with multicystic type dilatation, the mean amylase level in the gallbladder was 200,010 Somogyi Units, and the amylase level in the choledochal cysts could not be examined.

Pressure Measurements in the Biliary Tract Before and After Gastrin Stimulation

Before gastrin stimulation the mean pressures in the duodenum and sphincter of Oddi were 9.4 ± 1.2 cm H_2O and 32.0 ± 3.7 cm H_2O, respectively (Table 4). The difference between the sphincter of Oddi pressure and the duodenal pressure was 22.8 ± 3.1 cm H_2O. The length of the high-pressure zone in the sphincter of Oddi was 1.6 ± 0.2 cm. The choledochopancreaticoductal junction pressure was 12.8 ± 1.6 cm H_2O.

The mean sphincter of Oddi pressure in the cystic type and in the fusiform type after gastrin stimulation was 45.4 ± 4.1 cm H_2O and 41.0 ± 3.3 cm H_2O, respectively. These values were significantly higher ($p < 0.05$, $0.05 < p < 0.1$) than before gastrin stimulation. However, there was no significant difference between these two types. The mean differences between sphincter of Oddi pressure and duodenal pressure in the cystic type and in the fusiform type after gastrin stimulation were 37.0 ± 4.2 cm H_2O and 34.0 ± 3.7 cm H_2O, respectively. These values were significantly higher ($p < 0.05$) than before gastrin stimulation. However, there was no significant difference between these two types. The mean lengths in the cystic type and in the fusiform type after gastrin stimulation were 1.6 ± 0.3 cm and 1.7 ± 0.2 cm, respectively. The choledochopancreaticoductal junction pressures in the cystic type and in the fusiform type after gastrin stimulation were 13.0 ± 1.1 cm H_2O and 13.5 ± 0.8 cm H_2O, respectively. Thus, tetragastrin stimulation caused no significant change in choledochopancreaticoductal junction pressures before and after gastrin stimulation.

Discussion

As the cause of choledochal cyst, Babbit[2] proposed an abnormal relationship between the common bile duct and

TABLE 4. *Pressure Measurements of Biliary Tract in Cystic and Fusiform Types Before and After Tetragastrin Stimulation*

	Duodenal Pressure (cm H_2O)	Sphincter of Oddi Pressure (cm H_2O)	Difference Between Sphincter of Oddi Pressure and Duodenal Pressure (cm H_2O)	Length of High-Pressure Zone (cm)	Choledochopancreaticoductal Junction Pressure (cm H_2O)
Before stimulation (n = 11)	9.4 ± 1.2	32.0 ± 3.7*†	22.8 ± 3.1‡	1.6 ± 0.2	12.8 ± 1.6
Cystic type after gastrin stimulation (n = 7)	8.4 ± 1.3	45.4 ± 4.1*	37.0 ± 4.2‡	1.6 ± 0.3	13.0 ± 1.1
Fusiform type after gastrin stimulation (n = 4)	7.0 ± 1.1	41.0 ± 3.3†	34.0 ± 3.7‡	1.7 ± 0.2	13.5 ± 0.8

Mean ± SE.
* $p < 0.05$.
† $0.05 < p < 0.1$.
‡ $p < 0.05$.

the pancreatic duct. Miyano et al[3] and Kimura et al[4] reported that all of the patients with choledochal cyst, except those with choledochocele, had an abnormal choledochopancreaticoductal junction. Komi et al[5] also reported the frequency of abnormal anomalous ductal union in patients with choledochal cyst to be 39%. In our series, 25 of the 26 patients (96.2%) with congenital choedochal dilatation had an abnormal choledochopancreaticoductal junction. Therefore, there is no denying the fact that choledochal dilatation has a close association with abnormal choledochopancreaticoductal junction, whether direct or indirect.

Types of abnormal choledochopancreaticoductal junction were analyzed in relation to the forms of choledochal dilatation. In our series, the C-P type was often found in the cystic type of choledochal dilatation, and the P-C type was often found in the fusiform type of choledochal dilatation. These results are consistent with those previously reported.[6,7] Therefore, the types of abnormal choledochopancreaticoductal junction seem to correlate well with the degree of choledochal dilatation.

The present study showed that the amylase levels in the choledochal cyst and the gallbladder were elevated regardless of the form of choledochal dilatation. These results indicate that a free reflux of pancreatic juice into the biliary system occurs in patients with congenital choledochal dilatation. In patients with the fusiform type of choledochal dilatation, the amylase level in the gallbladder was significantly higher than in the choledochal cyst. This result is natural, because the gallbladder is said to concentrate bile to between 10% and 20% of its original volume.[8]

Kimura et al.[4] stressed that regurgitation of pancreatic juice was an important factor in gallbladder carcinoma, especially in patients with anomalous pancreaticobiliary ductal union. In our series, we actually had a patient with adenocarcinoma, a 12-year-old girl with anomalous pancreaticobiliary ductal union. From these results, it seems reasonable to assume that the longstanding inflammation of the biliary tract caused by the reflux of pancreatic juice might be one of the factors in carcinogenesis in the biliary tract, especially in the gallbladder.

Intraoperative manometry showed a high-pressure zone in the area of the sphincter of Oddi in patients with congenital choledochal dilatation. However, no high-pressure zone was found in the area of the common channel or the choledochopancreaticoductal junction. This indicates that the influence of the sphincter of Oddi pressure does not extend to the area of the abnormal choledochopancreaticoductal junction. Gastrin increased the sphincter of Oddi pressure in patients with congenital choledochal dilatation. No increase of pressure was found in the area of the common channel or the choledochopancreaticoductal junction, however, even after the administration of gastrin. This indicates that the change in sphincter pressure caused by gastrin administration does not extend to the area of abnormal choledochopancreaticoductal junction.

These results suggest that a free reflux of pancreatic juice into the biliary system can occur, and this free reflux may be due to the lack of sphincter function at the junction of the common bile and pancreatic ducts.

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Management Strategies in Resection for Hilar Cholangiocarcinoma

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Between 1960 and 1990, resection was performed in 23 of 122 patients who underwent surgical treatment for hilar cholangiocarcinoma. Local excision of the lesion alone was performed in 10 cases (43%). Hepatic resection for tumor extending to the secondary bile ducts or hepatic parenchyma was performed in 13 cases (57%): extended right hepatectomy (3), right hepatectomy (1), extended left hepatectomy (6), left hepatectomy (2), and left lobectectomy (1). In three other cases, resection by total hepatectomy and liver transplantation was performed, but these were not included in the analysis of results for resection. Significant operative complications occurred in only two cases (8.7%), and the operative mortality rate was zero. In four cases, complete excision of the tumor could not be achieved macroscopically (macroscopic curative resection rate 19/122; 15.6%). In nine cases, the margins of the resected specimens were free from tumor on histologic examination (microscopic curative resection rate, 9/122; 7.4%). In 10 cases, the resection margins were found to contain tumor on histologic examination. The overall survival rate was 87% at 1 year, 63% at 2 years, and 25% at 3 years (median survival, 24 months). The survival and freedom from recurrence rates for patients with free resection margins was superior to that for patients with involved resection margins or residual macroscopic disease. A potentially curative resection, with histologically negative margins and no recurrence to date, was achieved in seven patients using the following procedures: local excision for two type I lesions; left hepatectomy plus excision of segment 1 for two type IIIb lesions and one type IV lesion; right hepatectomy and right hepatectomy plus excision of segment 1 for two type IIIa lesions. These results indicate that improved survival in hilar cholangiocarcinoma can be achieved by resection, with minimal morbidity and zero mortality rates, if histologically free resection margins are obtained. To achieve this, we recommend the following procedures for each type of lesion, based on our experience and on anatomic considerations: local excision for type I; local excision plus resection of segment 1 for type II; local excision, resection of segment 1, and right or left hepatectomy for types IIIa and b; hepatectomy plus liver transplantation for type IV.

IT IS NOW more than 25 years since the first reports of surgery for proximal cholangiocarcinoma involving the bile duct confluence, yet we still are confronted by many of the same questions and controversies regarding the management of this lesion.[1-10] Despite the fact that the lesion is usually slow growing, and does not have a high propensity for metastasis, the diagnosis is usually not made until the bile duct is occluded and the patient is jaundiced.[9,11] Even though the lesion may remain small, its location and close proximity to important structures in the hilum of the liver makes curative excision technically difficult and often impossible.[6,7,9,10] Thus, excision is associated with high reported operative morbidity and mortality rates, particularly when liver resection is also performed.[6,10] In addition, the results of excision, in terms of improvement of long-term survival, have been disappointing in most studies.[3,7,8,10] For these reasons, many recent reports recommend a palliative approach to management, using either surgical bypass or, more recently, percutaneous or endoscopic stent insertion, with or without radiotherapy, to achieve biliary decompression and alleviation of symptoms.[3,12-16]

There are reports, however, of long-term survival after excision, and several studies have suggested that, in a small but significant percentage of patients, improved survival after excision can be obtained.[4-10] In particular, the studies by Launois et al.,[4] Evander et al.,[5] Blumgart et al.,[6] and Reding et al.[17] have concluded that, in terms of length and quality of survival, excision offers the best form of treatment. Most of the controversy concerning excision to achieve a "cure" surrounds the ability of a local resection to completely remove all tumor tissue and thus significantly alter the natural history of the disease.[3] This is thought to be related principally to the tendency of the tumor to grow into the perineural tissue and thus spread for a considerable distance along the bile duct wall.[11,18] Histologic examination of resected specimens has demonstrated, in some studies, a positive correlation between

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absence of residual tumor in the resection margins and long-term survival.[7,10]

This has encouraged some authors to recommend a radical approach, including extensive liver resection and in some cases hepatectomy and transplantation.[8,10,19] Others have maintained that this indicates that the disease may be multifocal and that the addition of hepatic resection will not necessarily ensure that the resection margins are free from tumor.[3] Moreover, if hepatic resection is associated with significant operative morbidity and mortality rates, it may not produce any significant overall benefit.[3,10] Thus, in view of the diversity of opinion regarding resection to achieve a cure, this review was undertaken in an attempt to determine if resection has any beneficial effect in terms of alteration of the natural history of the disease, and also to allow us to develop guidelines for a more formalized approach for each type of lesion.

Patients and Methods

Patients

This study is based on 136 consecutive patients with hilar cholangiocarcinoma, treated at Hôpital Paul Brousse, Paris, between January 1960 and December 1990. Patients were assessed for surgical treatment using preoperative ultrasound, computed tomographic (CT) scan, celiac and mesenteric angiography, and assessment of general medical condition. One hundred twenty-two patients were considered suitable for surgical treatment.

In most cases, resection was only performed if it was considered as potentially curative, although in two cases, one with necrosis of the left hepatic lobe and one with a large tumor, excision was performed to obtain the most effective palliation. The potential for curative resection was assessed by intraoperative ultrasonography, intraoperative transhepatic cholangiography, and frozen section histologic examination. The disease was considered incurable if there was lymph node involvement outside the hepatic pedicle, intraperitoneal tumor spread, or distant metastases. Involvement of the main trunk of the portal vein or hepatic artery, bilateral tumor extension to the secondary hepatic ducts, or parenchymal spread within the two lobes of the liver also were considered to indicate incurable disease. Since the introduction of liver transplantation, however, contraindications to curative surgical treatment only exist with extrahepatic disease.

Using these criteria, 23 patients were considered suitable for resection and are the focus of the study (resectability rate, 19%). Details for each patient are given in Table 1. There were 12 men and 11 women, with a mean age of 50 years (range, 22 to 82 years; median, 48 years). All but five patients had been previously investigated or treated at another institution. Ten patients (43%) had undergone surgical exploration and drainage by a bilioenteric anastomosis or transtumoral intubation. Percutaneous external biliary drainage had been performed in one case, and in 2 cases, biliary drainage had been performed by endoscopic intubation. Patients considered unsuitable for resection after investigation were treated by surgical bypass or transtumoral intubation, if this had not already been performed.

Recently, three patients with type IV lesions have been treated by hepatectomy and liver transplantation. One of these patients had extension of the tumor to the middle third of the bile duct and also underwent a Whipple pancreaticoduodenectomy, 1 month after transplantation. These three patients were not included when analyzing results, however, because the main aim of the study was to concentrate on factors influencing survival after resection, without transplantation.

Anatomic Types

Tumors were divided into four anatomic types using a modification of the original Bismuth–Corlette classification (Fig. 1).[20] This classification was based on ultrasonic, cholangiographic, and macroscopic pathologic appearances at operation. There were three type I and three type II cases. Sixteen cases were type III; in nine of these, tumor extension involved the right hepatic duct (IIIa) and in seven it involved the left hepatic duct (IIIb). There were four type IV lesions.

Surgical Procedures

The surgical procedure undertaken depended on the intraoperative evaluation of the anatomic type of the lesion (Table 1). Local excision of the tumor and suprapancreatic bile duct was performed in 10 cases. Hepatic resection, for tumor extending to the secondary bile ducts or hepatic parenchyma, was required in 13 cases. The liver resections comprised one left lobectomy (segments 2 and 3), eight left hepatectomies, extended to include the caudate lobe (segment 1) in six cases, one right hepatectomy, and three extended right hepatectomies—to include segment 4 (one case), segment 1 (one case), or both segments 1 and 4 (one case).

In all cases, all lymphatic and areolar tissue in the hepatic pedicle was excised. Seven patients had local lymphatic spread at the time of surgery. In three, this was confined to the juxtatumoral nodes, and in four, the nodes in the hepatic pedicle were involved. Bilioenteric continuity was re-established using a Roux-en-Y loop of jejunum.

Histologic Findings

A histologic diagnosis was established in every case. The most frequent finding was an infiltrating cholangio-

TABLE 1. *Clinical, Pathologic, and Follow-up Details for Resection of Hilar Cholangiocarcinoma in 23 Patients*

Patient No.	Sex	Age (yr)	Intraoperative Classification	Surgical Procedure	Pathologic Group	Follow-up (mo)	Recurrence		Alive or Dead	Remarks
							Local	Distant		
1	F	33	IIIA	Excision	A	15	Yes	Yes	Dead	—
2	M	43	II	Excision	A	32	Yes	Yes	Dead	Portal vein invasion
3	M	22	II	Excision	A	6	Yes	Yes	Dead	Portal vein invasion
4	F	37	IIIb	Excision, left lobectomy	A	32	Yes	Yes	Dead	Left lobe necrosis
5	F	71	I	Excision	B	132	No	No	Dead	Papillary tumor
6	M	63	IIIa	Excision	B	38	Yes	Yes	Dead	—
7	M	58	IIIb	Excision, left hepatectomy + segment I	B	8	Yes	Yes	Dead	—
8	M	60	IIIb	Excision, left hepatectomy + segment I	B	24	Yes	Yes	Dead	—
9	F	63	IIIa	Excision, right hepatectomy + segments I + IV	B	16	Yes	Yes	Dead	—
10	M	36	IIIa	Excision	B	33	Yes	Yes	Dead	—
11	F	38	IIIb	Excision, left hepatectomy	B	32	No	Yes	Alive	Left liver atrophy
12	F	59	II	Excision	B	15	Yes	Yes	Dead	—
13	M	46	IIIa	Excision, left hepatectomy + segment I	B	17	Yes	No	Alive	—
14	F	55	IIIb	Excision, left hepatectomy	B	6	Yes	No	Alive	—
15	M	82	I	Excision	C	48	No	No	Alive	—
16	F	48	IIIa	Excision	C	14	Yes	Yes	Dead	—
17	M	43	IIIa	Excision, right hepatectomy + segment IV	C	22	Yes	Yes	Dead	—
18	M	56	I	Excision	C	39	No	No	Alive	—
19	F	63	IV	Excision, left hepatectomy + segment I	C	29	No	No	Alive	Left liver atrophy
20	F	41	IIIb	Excision, left hepatectomy + segment I	C	31	No	No	Alive	—
21	M	44	IIIb	Excision, left hepatectomy + segment I	C	30	No	No	Alive	Left liver atrophy
22	M	54	IIIa	Excision, right hepatectomy + segment I	C	15	No	No	Alive	—
23	F	61	IIIa	Excision, right hepatectomy + segment I	C	12	No	No	Alive	—

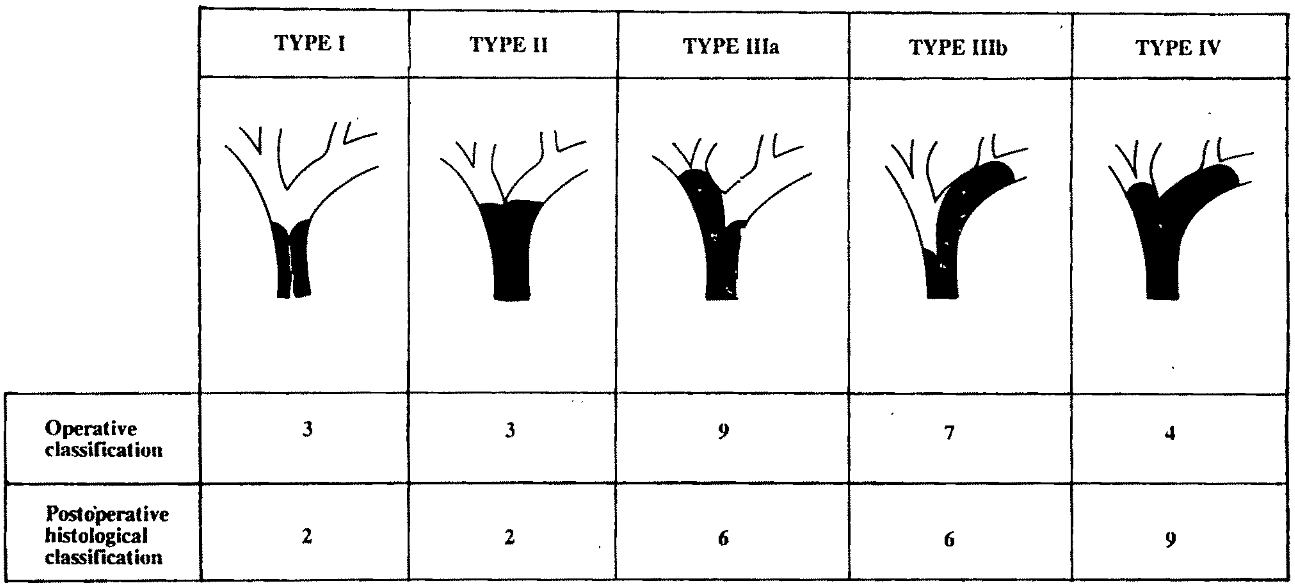
carcinoma (91%). In two patients, with recurrent lesions, malignancy was only confirmed at 3 and 5 years after the first biopsy was performed. In the first patient, the tumor was slow growing, without perineural infiltration, thus making histologic confirmation difficult. The second patient presented with a papillary tumor with polypoidal growth into the bile duct confluence. She survived for 11 years, free from recurrence, after several tumorectomies followed by excision of the bile duct confluence.

Based on macroscopic and microscopic appearances, patients were classified into three groups (Table 2). In four patients, complete excision of the tumor was not achieved macroscopically (Group A). In two of these, an extension of the tumor into the portal vein bifurcation was discovered during dissection. In one case, with partial necrosis of the left lobe of the liver, a left lobectomy and excision of the tumor was performed. In one other case, excision of the tumor was performed to allow an adequate bypass. Thus, of the 23 resections performed, a macroscopic curative resection was achieved in 19 (macroscopic curative resection rate 19/122; 15.6%).

The definitive histology report showed, in 10 cases, a microscopic extension of the tumor involving the surgical resection margins or lymph nodes outside the hepatic pedicle. These resections were retrospectively classified as being palliative (Group B). Thus, after histologic analysis, a potentially curative resection was performed in nine patients (Group C) (microscopic curative resection rate, 9/122; 7.4%). The reclassification of lesions, based on postoperative histologic findings, is detailed in Figure 1.

Outcome and Follow-up

Operative mortality was defined as death during or within 2 months after surgery. Follow-up ranged from 6 months to 11 years (mean, 26 months) and included clinical assessment, measurement of liver function tests, and ultrasound examination. A special emphasis was placed on the extension of the tumor at the time of resection (macroscopic or microscopic), the type of recurrence (local or distant), and the time interval between resection and recurrence. In addition, the time interval between local recurrence and death due to secondary spread was analyzed to focus, retrospectively, on patients who could pos-



	TYPE I	TYPE II	TYPE IIIa	TYPE IIIb	TYPE IV
Operative classification	3	3	9	7	4
Postoperative histological classification	2	2	6	6	9

FIG. 1. Modified Bismuth–Corlette classification of hilar cholangiocarcinoma in 26 patients, based on operative findings and postoperative histologic examination (3 patients who underwent liver transplantation included).

sibly have benefitted from an alternative surgical approach.

Results

Operative Morbidity and Mortality Rates

In all cases, excision of the tumor and restoration of bilioenteric continuity produced immediate relief of jaundice and disappearance of symptoms. Two patients developed a postoperative bile leak. The first, who had an extensive liver resection (6 segments), developed biliary peritonitis and required reoperation. The second developed an external biliary fistula, which closed spontaneously after 25 days. One patient developed a wound infection, and two developed a postoperative respiratory infection. No patient developed evidence of liver dysfunction secondary to a biliary stricture. There was no operative mortality.

Survival and Recurrence

The survival and recurrence rates for patients in groups A, B, and C are displayed in Table 1 and Figure 2. When analyzing survival figures, one patient was excluded. This was a 70-year-old patient who had a papillary type lesion and a prolonged survival (11 years), not typical of the remainder of the group. Death was due to cardiovascular disease.

TABLE 2. *Classification Based on Gross and Histologic Appearances*

Group	Pathologic Appearance	N
A	Gross residual tumor	4
B	Microscopic residual tumor at resection margins	10
C	Resection margins free from tumor microscopically	9

The overall survival rate was 87% at 1 year, 63% at 2 years, and 25% at 3 years. Mean survival was 25.5 months (median, 24 months). Currently, 10 patients are alive, 6 to 48 months after surgery, seven of them free from recurrence. All four group A patients died of recurrent disease within 32 months. In group B patients, the survival rate was 82% at 1 year, 43% at 2 years, and 12% at 3 years. The free-from-recurrence rate was 44% at 1 year, 22% at 2 years, and 0 at 3 years.

The survival rate in group C patients was 100% at 1 year, 71% at 2 years, and 50% at 3 years. Seven patients are currently alive, free from recurrence, including two patients with juxtatumoral lymph node involvement (29 and 39 months after surgery). One 82-year-old patient with juxtatumoral lymph node involvement survived for more than 4 years, free from disease, but was subsequently lost to follow-up. Two patients in group C died of recurrence of their tumor at 14 and 22 months postoperatively. One of these, operated on early in the series, had a resection of a type IIIa tumor with resection of the hilar plate, but no liver resection. She presented at 10 months postoperatively with evidence of recurrence at the anastomosis and in the hepatic pedicle. The other patient, with a type IIIa lesion with pedicle lymphatic involvement, was treated by resection and extended right hepatectomy. He died of disseminated spread of the tumor. In group C, there was a trend toward improved long-term survival because survival and free-from-recurrence rates were similar at 2 and 3 years (Fig. 2).

Correlation Between Histologic Findings and Tumor Progression

There was a good correlation between histologic findings and progression of the disease. Microscopic extension of the tumor to the resection margin was associated with local recurrence in all cases except one. In addition, local recurrence was not observed in any cases when the resection margin was free from tumor on histologic examination.

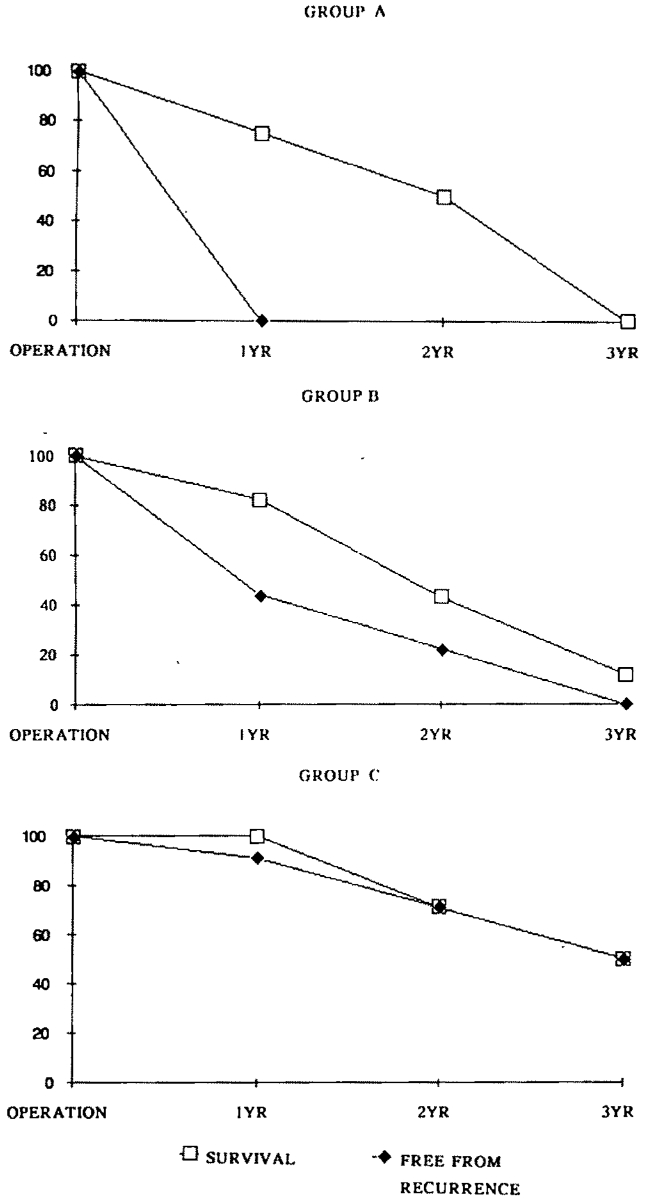


FIG. 2. Survival and recurrence-free rates (percentage) for patients in groups A, B, and C.

Effect of Local Lymphatic Involvement at the Time of Surgery

Local lymphatic involvement, either juxtatumoral or in the hepatic pedicle, was present in seven patients. Three patients with free resection margins but juxtatumoral nodal involvement were free from recurrence at 29, 39, and 48 months. Four patients (three with tumor invasion of the resection margin) with nodal involvement in the hepatic pedicle all presented with multifocal recurrence. Thus, local lymph node involvement, as a single factor, did not appear to influence outcome and was less important than microscopic involvement of the resection margins.

Temporal Relationship Between Surgery, Recurrence, and Death

The time interval between surgery and evidence of recurrence (either symptomatic or detected by investigation) was variable, ranging from 1 to 26 months. In group A patients, the free-from-recurrence period ranged from 1 to 11 months (mean, 4.5 months). In group B patients, this period ranged from 1 to 26 months (mean, 14 months). The mean time interval between recurrence and death was 8 months. In group C, recurrence (two patients) was at 10 and 20 months.

Local recurrence was present long (>15 months) before metastases occurred in four patients; three group B patients with microscopic residual tumor in the bile duct and one group A patient. These patients (one type II, three type III) all underwent local excision. In retrospect, it is possible that more extensive resections may have achieved a cure or prolonged survival.

Assessment of Curability of Resection

The extent of the surgical procedure and the effect on the development of local recurrence was assessed for each type of lesion. The four patients with macroscopic residual tumor were not included in this analysis. Three patients, who were found on postoperative histologic examination to have lymphatic involvement other than the local nodes, were also excluded as, in these cases, there was already distant spread and recurrence was always associated with distant metastasis. Total excision of tumors with local spread only was achieved in 16 patients (Table 3).

Local excision, without liver resection, was performed in eight cases. Three of these were type I lesions. In two of these, the resection margins were histologically negative, and neither developed local recurrence. In the third, prolonged survival (11 years), without recurrence, was achieved after several tumorectomies and subsequent bile duct excision. The other five cases (two type II, three type IIIa) all had macroscopic or microscopic involvement of

TABLE 3. *Assessment of Curability of Resection for Tumors With Local Spread Including Juxtatumoral Lymphatic Involvement*

Surgical Procedure	N	Free From Recurrence	Local Recurrence	Distant Metastasis
Local excision				
Type I	3	3		
Type II	2	1	1	
Type IIIa	3		1	2
Liver resection				
Left hepatectomy + segment 1				
Type IIIb	4	2	1	1
Type IIIa	1		1	
Type IV	1	1		
Right hepatectomy				
Type IIIa	1	1		
Right hepatectomy + segment 1				
Type IIIa	1	1		

the resection margins and all developed local recurrence. Thus, local excision of the lesion, without liver resection, achieved free resection margins and prevented local recurrence in type I lesions only.

Local excision plus liver resection was performed in eight cases. Six patients (four type IIIb, one type IIIa, one type IV) underwent a left hepatectomy plus excision of segment 1. Three of these patients (two type IIIb, one type IV) had histologically negative resection margins and are free from recurrence. Two patients (both type IIIa) underwent right hepatectomy (one patient also had excision of segment 1). In each of these, the resection margins were histologically negative and neither developed local recurrence. Thus, in eight patients with type III or IV lesions, in whom local excision of the lesion was accompanied by liver resection, only three developed local recurrence.

Therefore, a potentially curative resection, with histologically negative resection margins and no evidence of recurrence to date, was achieved in eight cases using the following procedures: local excision for three type I lesions; left hepatectomy plus excision of segment 1 for two type IIIb lesions and one type IV lesion; right hepatectomy and right hepatectomy plus excision of segment 1 for two type IIIa lesions.

Discussion

When analyzing our survival figures, it was important to assess patients according to the potentially curative nature of the resection. As expected, in patients in whom a macroscopic clearance of the tumor was not achieved (group A), there was no improvement in survival and all patients died, within 32 months, of progression of their disease. In cases where the tumor was completely excised macroscopically but where, on microscopic examination, the resection margins were still found to be involved (group B), the survival and free-from-recurrence figures were superior to those for patients in group A. Moreover, when patients in whom the resection margins were clear (group C) were analyzed, the survival and free-from-recurrence figures were superior to those of the other two groups. Thus, these results suggest that by completely excising the lesion it is possible to alter the natural history in terms of progression of the disease and long-term survival. The difference between groups B and C, however, illustrates that to achieve a curative resection, removal of all tumor tissue, with free resection margins, must be obtained. This emphasizes the importance of extensive preoperative and perioperative assessment so that resection is only performed when potentially curative and inappropriate extensive resection is avoided (*i.e.*, to achieve a microscopic curative resection rate equal to the overall resection rate).

The second aim of this study was to determine the exact type of surgical procedure needed in each particular case, to ensure a radical resection and thus a potential cure. This clearly relates to the controversy as to whether liver resection, and if so what type, should be added to local excision.[3,8,10]

Local excision of the lesion was performed in eight cases with local spread of the tumor only. Five of these patients developed local or distant recurrent disease. The only patients who had negative resection margins and were free from recurrence after local excision were those with type I lesions, in other words, confined to the bile duct confluence but not involving the superior aspect. Thus, it seems that local excision without hepatic resection is sufficient for type I lesions only.

In two type II cases, in which local excision was performed, both had involvement of the resection margins (one microscopic; one macroscopic) and both developed early recurrent disease. In type II cases, there is no communication between the right and left duct systems on the cholangiogram, and the superior aspect of the biliary confluence is involved. In this situation, the biliary ducts draining the caudate lobe (segment 1) are almost inevitably involved by tumor,[21] and for these lesions local excision of the tumor probably always will need to be accompanied by resection of the caudate lobe. For some large type II lesions, tumor extension may involve the parenchyma of segment 4, and resection of segment 4 also may be necessary.

When the lesion involves the superior aspect of the biliary confluence and extends into one of the main hepatic ducts (type IIIa or IIIb), a radical tumor clearance can not be achieved by local excision because there inevitably will be ductal involvement of the caudate lobe and the secondary bile ducts on the involved side.[21] Three of our patients with type III lesions who were treated by local excision had residual disease, and all developed recurrence. In contrast, in four of the seven patients with type III lesions, who underwent local excision plus hepatectomy, free resection margins and no evidence of recurrence were achieved. Thus, it seems that for type III lesions, treatment should consist of local excision and resection of the caudate lobe plus resection of the hepatic segments drained by the involved duct; in other words, a right hepatectomy for type IIIa lesions and a left hepatectomy for type IIIb lesions. For some large type IIIa lesions, with tumor extension involving the parenchyma of segment 4, resection of segment 4 also may be necessary (one case in our series).

In these patients, the feasibility of extensive liver resection depends on the remaining volume of functioning hepatic parenchyma and, in particular, an extended right hepatectomy for a type IIIa lesion may not leave sufficient functioning parenchyma. In some cases, however, tumor extension with involvement of the major branch of the hepatic artery or portal vein may result in unilateral liver atrophy, with corresponding hypertrophy of the other hemiliver, thus making a major liver resection possible. In some cases, with deteriorating preoperative liver function or sepsis, preoperative percutaneous transhepatic biliary drainage may be indicated to improve hepatocellular function and reduce the risk of liver failure in the immediate postoperative period. Although prospective studies of this technique in patients with obstructive jaundice from various causes have failed to demonstrate any significant overall benefit,[22,23] Nimura et al.[21] advocate its use routinely before liver resection in patients with hilar cholangiocarcinoma, and we have found it useful in certain selected cases. There may be some type III cases without hypertrophy of the uninvolved hemiliver, however, in which, despite optimal preoperative drainage and preparation, resection would be associated with a very high risk of postoperative liver failure. In these cases, liver transplantation may be indicated.

When the tumor has extended to involve the secondary bile ducts or hepatic parenchyma bilaterally, or the main trunk of the hepatic artery or portal vein (type IV), resection techniques almost always fail to achieve a radical excision of all tumor tissue, although in one of our patients with a type IV lesion, which involved principally the left side, histologically free resection margins were obtained. She has survived more than 3 years, free from recurrence, after excision of the tumor plus a left hepatectomy and excision of the caudate lobe. For type IV lesions, hepatectomy and liver transplantation may be indicated. This offers the only chance of complete tumor removal and potential cure in these cases, although results have generally been poor, with a high incidence of tumor recurrence.[24,25] One of our three patients treated by transplantation developed recurrence in the hepatic pedicle, 8 months after transplantation. Results from Pichlmayr et al.[19] are more encouraging, particularly for patients treated in recent years.

We believe from our results that it is justifiable to conclude that long-term survival can be achieved in selected cases of hilar cholangiocarcinoma by adopting a policy of tumor excision, with liver resection if required, to obtain tumor-free resection margins. Consequently, based on our findings and anatomic considerations of the hepatic hilus, we now perform local excision for type I; local excision plus resection of segment 1 for type II; local excision, resection of segment 1, and right or left hepatectomy for types IIIa and IIIb and hepatectomy plus liver transplantation for type IV lesions. We believe that this formalized type of approach provides the best chance of achieving a curative resection and providing improved long-term results. The very low morbidity and mortality rates that may be achieved with these procedures also justify the "attempt at cure" and counters any arguments in favor of a minimal palliative approach.

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The Surgical Spectrum of Hereditary Pancreatitis in Adults

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The role of operative intervention for hereditary pancreatitis, a rare form of chronic parenchymal destruction, is unclear. To determine whether surgical therapy is safe and provides prolonged symptomatic relief, the authors reviewed the management of 22 adults (11 men, 11 women) with hereditary pancreatitis treated surgically between 1950 and 1989. Hereditary pancreatitis was defined as a family history of two or more relatives with pancreatitis and clinical, biochemical, or radiologic evidence of pancreatitis. The mean ages at onset of symptoms and at operation were 15 years (range, 3 to 52 years) and 31 years (range, 18 to 54 years), respectively. Pain was the primary indication for operation in all patients. Additional symptoms included nausea, vomiting (73%), weight loss (55%), and diarrhea (41%). Ductal dilatation was present in 68%, pancreatic parenchymal calcifications in 73%, pseudocysts in 36%, and splenic vein thrombosis in 18%. Primary operations included ductal drainage in 10 patients, pancreatic resection alone in three, resection with drainage in three, cholecystectomy plus sphincteroplasty in two, cholecystectomy with or without common bile duct exploration in two, pancreatic abscess drainage in one, and pseudocyst drainage in one. There were no perioperative deaths, and the morbidity rate was 14% (intra-abdominal abscess, wound infection, and urinary tract infection). Symptoms recurred in nine patients. Severity prompted reoperation in five. Secondary operations included pancreatic resection in three, pseudocyst excision in one, and pancreaticolithotomy in one. Follow-up to date is complete and extends for a median of 85 months. Eighteen patients (82%) are clinically improved or asymptomatic. Symptoms have persisted in four patients, and two patients have died of pancreatic carcinoma. Two patients died of unrelated causes. Surgical therapy for patients with hereditary pancreatitis selected on the basis of the traditional indications for surgical treatment of chronic pancreatitis is safe and efficacious.

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HEREDITARY PANCREATITIS, ALSO termed familial pancreatitis, is a rare form of chronic progressive pancreatic inflammation and parenchymal destruction associated with a variable clinical course. This entity, first described in 1952,[1] is inherited as a non–sex-linked autosomal dominant trait with incomplete penetration. Most previous reports have detailed the clinical features of this disease.[2-11] Few articles have focused on the role of operative intervention in the treatment and prevention of future complications arising from hereditary pancreatitis.[12,13] Although the indications for surgical treatment of patients with chronic pancreatitis related to other causes have been widely discussed and generally accepted, the indications for operative intervention in hereditary pancreatitis have not been defined clearly, especially with regard to efficacy in the permanent relief of chronic abdominal pain, or in the prevention of pancreatic malignancy, or in relief of recurrent exacerbations of acute pancreatitis.

Previous reports of surgical treatment of hereditary pancreatitis have been largely anecdotal because of the infrequent occurrence and limited clinical experience with this disease. The aim of this study was to review the broad experience at one institution with the surgical spectrum of hereditary pancreatitis in adults to assess immediate and long-term results of operative therapy.

Methods

The medical records of all patients evaluated from 1950 to 1990 with documented hereditary pancreatitis were reviewed. Hereditary pancreatitis was defined as biochemical or radiographic evidence of acute and recurrent, or chronic pancreatic inflammation and a family history of two or more relatives with documented pancreatitis. Eighty individuals representing more than 20 kindreds were identified; adults (aged >18 years) who underwent surgical intervention at Mayo Medical Center were se-

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lected for inclusion in this review. Medical records were analyzed with reference to age of onset of symptoms, age of operative intervention, spectrum of clinical presentation, preoperative management, and diagnostic evaluation. Operative therapy was categorized according to surgical procedure, pathologic review, perioperative morbidity, and long-term clinical results. Follow-up information to date (median, 85 months; range, 8 to 474 months) was obtained by telephone interview, return evaluation, or by written correspondence.

Results

Patient Population

Twenty-two patients (11 men, 11 women) were treated by surgical intervention at an average age of 31 years (range, 18 to 54 years). The average age of onset of symptoms was 15 years (range, 3 to 52 years). The indications for operation are shown in Table 1. All but one patient were taking narcotics for chronic persistent or episodic recurrent abdominal pain; one patient had undergone celiac plexus blockade. Most patients also had experienced repeated clinical episodes of acute pancreatitis.

Preoperative Evaluation

Hyperamylasemia was present in 55% of patients and usually correlated with concurrent acute pancreatitis. Pancreatic exocrine and endocrine insufficiency were present in 11 and three patients, respectively.

Objective radiographic imaging was performed in 19 patients and included computed tomography (CT) in 10, ultrasonography in nine, and endoscopic retrograde cholangiopancreatography (ERCP) in 13. The three patients who underwent only plain abdominal radiographs were managed before 1974 when the objective imaging tests became available. Pancreatic calcification was evident in 16 patients (73%). Ductal dilatation was noted in 15 patients (68%), concurrent ductal stones in 12 (55%), and pseudocysts in eight (36%). Of note was the presence of splenic vein thrombosis in four patients (18%).

TABLE 1. *Indications for Operative Treatment in 22 Patients With Hereditary Pancreatitis*

Indication	No. of Patients
Pain	22*
Chronic, persistent	10
Episodic, intermittent	11
Acute	1
Nausea/vomiting	16
Weight loss	12
Diarrhea	9

* All but the one patient with acute pain related to a pseudocyst required intermittent or chronic narcotics.

TABLE 2. *Initial Operative Treatment in 22 Patients With Hereditary Pancreatitis*

Treatment	No. of Patients
Pancreaticojejunostomy	13*
Distal pancreatectomy	3
Cholecystectomy with sphincteroplasty	4
	2
Enteric drainage pseudocyst	1
Debridement/drainage of pancreatic abscess	1
Total	22

* Three patients had concomitant distal pancreatectomy.

Operative Treatment

The initial operative approach, outlined in Table 2, involved primary pancreatic ductal drainage in 13, distal pancreatic resection in three, cholecystectomy in four, enteric drainage of a pseudocyst in one, and management of a pancreatic abscess in one. There were no hospital deaths. Significant complications occurred in two patients, including an intra-abdominal abscess and a pleural effusion in one each; both were managed by percutaneous drainage. One additional patient developed a wound infection. Median hospital stay was 13 days (range, 7 to 40 days).

Ductal Dilatation. Fifteen patients had pancreatic ductal dilatation (mean, 1.1 cm) confirmed either at ERCP or intraoperatively. A primary ductal drainage procedure (pancreaticojejunostomy) was performed in 11, two of whom had a concomitant distal pancreatectomy (Table 3). Although seven have remained asymptomatic, symptoms recurred in four, necessitating pancreatic resection in two (pancreatoduodenectomy, distal pancreatectomy), who have since remained asymptomatic. Primary pan-

TABLE 3. *Operative Procedure According to Status of the Pancreatic Duct*

	Persistent Pain Relief	
	Ductal Dilatation (15 patients)	Small Duct (7 patients)
Pancreaticojejunostomy	7/10*	
Distal pancreatectomy and proximal pancreaticojejunostomy	1/1	2/2†
Distal pancreatectomy	2/2	0/1†
Other		
Pseudocyst drainage	0/1‡	
Cholecystectomy		
Alone	—	1/2
With sphincteroplasty	—	1/2
Pancreatic drainage abscess	1/1	

* Two patients subsequently required resection.

† The patient without relief of symptoms went on to completion (total) pancreatectomy without success.

‡ Pseudocyst recurred requiring pancreatic resection.

creatic resection was successful in two patients (distal pancreatectomy in both). One patient with a pseudocyst was treated by cystoenteric drainage alone but had recurrence of both symptoms and the pseudocyst; he was treated successfully with distal pancreatic resection including the pseudocyst. The last patient presented with a pancreatic abscess that was managed by debridement and peripancreatic drainage. Although a dilated duct was noted on CT scan, ductal-enteric drainage was not performed, and he has done well.

Nondilated Small Duct. Three of the seven patients without major ductal dilatation underwent distal pancreatectomy. Symptoms recurred in one patient; despite completion (total) pancreatectomy, he remains symptomatic. The other four patients underwent cholecystectomy combined with sphincteroplasty in two for the possibility of exacerbation of acute pancreatitis by gallstones, which were found in only one patient; symptoms persisted in two patients, one of whom was later found to have pancreatolithiasis and an unresectable pancreatic cancer.

Long-term Results

Follow-up was complete in all patients at a median of 84 months (range, 8 to 474 months). Complete relief or definite, marked improvement in symptoms was maintained in 18 patients (82%), five of whom, however, had required reoperation. Symptoms have progressed in four patients, two of whom require narcotics on an intermittent basis for recurrent abdominal pain. Three of these four patients with recurrent symptoms had experienced chronic persistent pain preoperatively. Seven patients were treated with celiac plexus blocks at some point during their course; only one described a significant long-term benefit. Exocrine insufficiency developed in two of the 11 patients without steatorrhea at the time of initial presentation, and endocrine insufficiency developed in four of 19 patients without glucose intolerance initially. Two patients developed pancreatic adenocarcinoma, one of whom had a very strong family history of pancreatic cancer in that *both* parents had died of the disease.

Discussion

Our study shows that selected patients with chronic pain related to complications of hereditary pancreatitis can benefit from operative management. Although this is a relatively small (22 patients) and retrospective study, it represents the largest, comprehensive surgical series in the literature and thereby allows our conclusions to be based on more than anecdotal experience.

Although hereditary pancreatitis is known to be a disease associated with progressive parenchymal destruction, the complications and symptoms that develop share many similarities with chronic pancreatitis of other origins.[2–13] This form of pancreatic injury can present as a spectrum of recurrent episodes of acute pancreatitis, pseudocyst formation, pancreatic necrosis and abscess (although this is unusual), and chronic pancreatitis. In addition, patients with hereditary pancreatitis represent a spectrum of clinical presentations both in severity and in the complications that develop. Because of this varied clinical picture, our experience suggests that surgical evaluation should be assessed selectively in accordance with the criteria established for operative intervention in patients with pancreatitis of other causes.

Numerous series of the surgical treatment of chronic pancreatitis have generated a relative consensus among surgeons concerning the indications for operative treatment.[14–17] These indications include intractable chronic pain that interferes with lifestyle and work and local complications such as biliary or duodenal obstruction, symptomatic pseudocyst, pancreatic infection, and gastric variceal hemorrhage related to splenic vein thrombosis (sinistral portal hypertension). Using these criteria for operative treatment in our group of patients with hereditary pancreatitis, we achieved results very similar to those reported in the literature for chronic pancreatitis of other causes.

The most controversial aspect of this entity involves operative intervention in patients with chronic pain. Several groups have argued against operative therapy solely to relieve pain,[18,19] in view of the fact that chronic pain will eventually (over years) resolve or improve in most all patients.[18] In contrast, we[20] and others[14,15] believe that operative therapy is warranted in selected individuals in whom the pain is intractable and chronically persistent, is nonresponsive to celiac plexus block,[21] requires narcotics, and prevents a satisfactory lifestyle. Our patients with hereditary pancreatitis who underwent operative intervention primarily for pain were all taking narcotics and had failed all attempts at medical management. Although five patients (23%) required repeat operation for recurrent or persistent symptoms, we believe that our results justify this approach because 18 of 22 patients (82%) had persistent relief of incapacitating pain. Operative mortality rate was zero, and a significant morbidity rate was acceptable (14%) without long-term sequelae. These data correlate well with our experience[20,22] and that of others[14,15] with operative therapy in patients with chronic pancreatitis of other causes.

Our operative strategy in these patients with hereditary pancreatitis was generally dictated by the anatomy of the pancreatic duct. Most patients with dilated pancreatic ducts (≥8 mm) were treated by ductal drainage procedures (occasionally including a distal pancreatectomy), with intent of preserving pancreatic parenchyma and thus endocrine or exocrine function. With this operative approach, seven of 11 patients have done well; these results agree closely with previously published experience with nonhereditary chronic pancreatitis with long-term follow-up.[17,19,20] The seven patients with a "small" (nondilated) duct underwent several different operations. Three of these seven patients were treated by pancreatic resection, with good results in two patients. The third patient eventually underwent total pancreatectomy without relief of symptoms. We[20] and others[19] have also found that, despite removal of all chronically inflamed pancreatic tissue, the pain syndrome often persists. This may be related to poor patient selection because of either the confounding sequelae of chronic narcotic addiction or a poorly understood pain syndrome, possibly related to the perineural inflammation and proliferative neuropathy associated with chronic pancreatitis.[23] Interestingly, three of four patients who continue to have persistent pain postoperatively had persistent pain preoperatively, suggesting the individuals without pain-free intervals may be expected to have a less successful outcome after operative treatment. Four other patients underwent a primary cholecystectomy with or without sphincteroplasty, in which stones were found in only one patient. We doubt, in retrospect, whether the cholecystectomies were therapeutic.

It is noteworthy that none of our patients underwent proximal pancreatic resection as the surgeon's primary operative choice, presumably because no patient was considered to have most of the disease process localized to the head of the pancreas. Current surgical trends have veered away from staged distal pancreatectomies (80% or 95% resections) to proximal pancreatic resection, especially when there is an inflammatory mass in the head of the gland,[24,25] hypothesizing that the "pacemaker" of the disease resides in the head of the gland.[26] Whether our patients would have benefitted by proximal pancreatectomy remains speculative. Similarly, the role of pancreatic denervation,[27,28] segmental autotransplantation,[29] or autoislet cell transplantation[30] in this patient population is undefined.

A potentially important consideration when planning pancreatic operative intervention in patients with hereditary pancreatitis is the reputed increased incidence in the development of pancreatic carcinoma. Several authors have claimed this incidence to be as great as 20%.[2,11,12,31] Two of our twenty-two patients (9%) have developed pancreatic adenocarcinoma, one of whom was the daughter of parents who both died of pancreatic cancer. This unfortunate patient raises the question of whether an increased risk of malignant transformation justifies the acute and long-term morbidity and mortality rates of total pancreatectomy. Although this question remains unanswered, total pancreatectomy should be strongly entertained in the select group of patients with a clear family history.

Admittedly, our study did not address the overall frequency of patients with hereditary pancreatitis who were selected for operative treatment. In this respect, our patients represent a highly selected group. This experience does, however, confirm the efficacy of operative treatment in this group. Future studies will be required to identify the full spectrum of patients with hereditary pancreatitis who may benefit from operative therapy.

In summary, our approach and long-term results with the operative management of patients with surgical complications of hereditary pancreatitis agrees quite closely with operative results in patients with nonhereditary chronic pancreatitis. One must be cautious in comparing these results with the results in patients with nonhereditary chronic pancreatitis, most often of primary alcoholic origin. This latter group tends to be older and systemically debilitated compared with patients with hereditary pancreatitis.[14,18-20] Nevertheless, our results suggest that operative intervention in patients with surgical complications of hereditary pancreatitis can be based on the commonly accepted criteria used in patients with nonhereditary chronic pancreatitis. Because these patients tend to be younger and carry the burden of an increased risk of pancreatic carcinoma, a more aggressive resective approach may be entertained in selected patients.

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A Better Model of Acute Pancreatitis for Evaluating Therapy

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Existing models of acute pancreatitis have limitations to studying novel therapy. Whereas some produce mild self-limited pancreatitis, others result in sudden necrotizing injury. The authors developed an improved model providing homogeneous moderately severe injury by superimposing secretory hyperstimulation on minimal intraductal bile acid exposure. Sprague-Dawley rats (n = 231) received low-pressure intraductal glycodeoxycholic acid (GDOC) at very low (5 or 10 mmol/L) concentrations followed by intravenous cerulein. Cerulein or GDOC alone caused only very mild inflammation. However, GDOC *combined* with cerulein was uniformly associated with more edema ($p < 0.0005$), acinar necrosis ($p < 0.01$), inflammation ($p < 0.006$), and hemorrhage ($p < 0.01$). Pancreatic injury was further increased and death was potentiated by increasing volume and duration of intraductal low-dose GDOC infusion. There was significant morphologic progression between 6 and 24 hours. The authors conclude that (1) combining minimal intraductal bile acid exposure with intravenous hyperstimulation produces homogeneous pancreatitis of intermediate severity that can be modulated at will; (2) the injury is progressive over at least 24 hours with finite mortality rate; (3) the model provides superior opportunity to study innovative therapy.

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THE SPECTRUM OF human acute pancreatitis ranges from mild edematous disease that usually heals without intervention to severe hemorrhagic necrotizing inflammation that is often fatal. Whereas early death is caused by shock, most patients now survive this phase of the illness and succumb later to sepsis and multiple organ failure.[1-4] The extent of pancreatic and peripancreatic necrosis appears to be the principal determinant of lethal septic complications.[5] Because tissue necrosis evolves over a period of days after the onset of the disease,[6] there may be a window of opportunity early in the evolution of pancreatitis when appropriate intervention could prevent or reduce further injury. Yet no therapy has proven clinically effective against the necrotizing process.

Despite significant merits of existing models for elucidating the mechanisms involved in early cellular events and pathogenesis of acute pancreatitis, these models have not lent themselves to the development of effective new therapies. Further progress seems to be hampered by limitations of existing animal preparations.

An ideal model of acute pancreatitis should be reproducible, resemble the morphology and time course of human pancreatitis, and should be of a degree of severity such that a significant effect of treatment is easily demonstrable. Previously used models, including cerulein hyperstimulation[7] and traditional techniques employing infusion of highly concentrated bile salts into the pancreatic duct, suffer shortcomings of being either too mild or too catastrophic to be altered.[8-10] Pancreatitis induced by ethionine-supplemented, choline-deficient (CDE) diet may mimic the pace of human disease,[11] but also results in extreme injury, has a variable onset, and must be applied in young female mice, whose small size causes considerable technical limitations for rescue efforts.

Herein we characterize a method of producing acute pancreatitis in the rat that we believe overcomes the shortcomings of previous pancreatitis models. The combination of low-dose intraductal glycodeoxycholic acid (GDOC) and intravenous cerulein reproducibly causes an

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Preliminary results of this study have been presented at the 22nd Meeting of the European Pancreatic Club, Basel, Switzerland, October 15–17, 1990, and at the Annual Meeting of the American Pancreatic Association, Chicago, November 8–9, 1990.

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evolving homogeneous injury with a moderate degree of acinar necrosis, resembling the morphology of human pancreatitis. This model appears to be superior for the study of innovative therapy aimed at preventing or limiting the necrotizing phase of pancreatitis.

Materials and Methods

Animals

The 231 male Sprague-Dawley rats (350–450 g) used were housed individually in hanging wire-bottomed cages in rooms maintained at 21 ± 1 C using a 12-hour dark cycle. The animals were given a standard rat chow and fasted overnight before the experiment with water allowed *ad libitum.* Care was provided in accordance with the procedures outlined in the "Guide for the Care and Use of Laboratory Animals," (NIH Publication #85-23, 1985). The study was approved by the subcommittee on research animal care at our institution.

Anesthesia and Catheter Placement

Surgical anesthesia was induced with vaporized ether and maintained by an intraperitoneal injection of pentobarbital (20 mg/kg, Anthony Products, Arcadia, CA 91006) and ketamine (40 mg/kg, Ketalar, Parke-Davis, Morris Plains, NJ 07950). One day before the experiment, the right internal jugular vein was cannulated using soft polyethylene tubing (Silastic, inner diameter [ID] 0.02 inches, Dow Corning, Midland, MI 48640). Another catheter (Intramedic, ID 0.023 inches, Clay Adams, Parsippany, NJ 07054) was placed in the left carotid artery for blood sampling and pressure monitoring. Both catheters were tunneled subcutaneously to the suprascapular area and brought out through a flow-through tether, which permitted hemodynamic monitoring of the unrestrained conscious animal.

The next morning, the animals were transferred to the laboratory and allowed to adapt to the new environment for 30 minutes with noise and visual stimuli kept to a minimum. The catheters were connected to pressure transducers (Spectramed, Oxnard, CA 93030), and baseline hemodynamic and laboratory measurements were taken.

Induction of Pancreatitis

The animals were given a short-acting anesthesia (pentobarbital 10 mg/kg, ketamine 50 mg/kg), and the abdomen was opened by a midline incision. The duodenum and the common bile duct were identified, and the duodenal wall was punctured at its antimesenteric aspect with a 24-gauge Teflon catheter (Critikon, Tampa, FL 33630). The catheter was advanced into the common biliopancreatic duct for 5 mm (there is no main pancreatic duct in the rat) through the papilla of Vater. A fine 6–0 prolene suture was placed around the cannula at the duodenal wall to prevent backflow. Special attention was focused on atraumatic surgical technique. Perforation of the duct during cannulation and intrapancreatic hemorrhage during surgical manipulations were absolute criteria for exclusion (n = 18). The upper portion of the animal was then elevated 60 degrees for 5 minutes (with the duct cannula in place) to allow the duct system to empty of bile and pancreatic juice (drained volume, 0.05 to 0.15 mL). During the last 2 minutes of this procedure, the main hepatic duct was clamped just below the liver to facilitate complete drainage of pancreatic secretions. This clamp remained in place throughout the intraductal infusion to prevent misdirected flow into the biliary system.

The animals were randomly allocated to 12 groups (n > 12) (Table 1). Freshly prepared glycodeoxycholic acid (GDOC, Sigma, St. Louis, MO 63178, #G-3258) in glycylglycine-NaOH–buffered solution (pH 8.0, room temperature) at low (5 or 10 mmol/L) or high (34 mmol/L) concentrations then was infused over the assigned period in groups 2 through 3 and 5 through 12 at a pressure of 30 mmHg controlled by mercury manometer with the volume controlled by means of an interposed scaled glass tube. In saline controls (group 1) and cerulein controls (group 4), isotonic saline was infused intraductally instead of GDOC. The infusion was considered successful only if 0.1 to 0.15, 0.2 to 0.25, or 0.5 to 0.55 mL of the corresponding solution entered the common biliopancreatic

TABLE 1. *Control and Experimental Regimens*

Group	Intravenous Infusion	Intraductal Infusion	ID Volume ID Duration	Observation Period
1	Saline	Saline	0.1–0.15 mL 1.5 min	6 hr
2	Saline	GDOC 5 mmol/L	0.1–0.15 mL 1.5 min	6 hr
3	Saline	GDOC 10 mmol/L	0.1–0.15 mL 1.5 min	6 hr
4	Cerulein 5 μg/kg/hr	Saline	0.1–0.15 mL 1.5 min	6 hr
5	Cerulein 5 μg/kg/hr	GDOC 5 mmol/L	0.1–0.15 mL 1.5 min	6 hr
6	Cerulein 5 μg/kg/hr	GDOC 10 mmol/L	0.1–0.15 mL 1.5 min	6 hr
7	Saline	GDOC 34 mmol/L	0.1–0.15 mL 1.5 min	6 hr
8	Cerulein 5 μg/kg/hr	GDOC 10 mmol/L	0.2–0.25 mL 2.5 min	6 hr
9	Cerulein 5 μg/kg/hr	GDOC 10 mmo/L	0.5–0.55 mL 10 min	6 hr
10	Cerulein 5 μg/kg/hr	GDOC 10 mmol/L	0.1–0.15 mL 1.5 min	24 hr
11	Cerulein 5 μg/kg/hr	GDOC 10 mmol/L	0.2–0.25 mL 2.5 min	24 hr
12	Cerulein 5 μg/kg/hr	GDOC 10 mmol/L	0.5–0.55 mL 10 min	24 hr

ID, intraductal; GDOC, glycodeoxycholic acid.

duct (Table 1). If the infusion volume was reached faster than the predetermined infusion time, the infusion was stopped when the required volume had entered the duct, but the infusion system remained in place to allow intraductal exposure to the infusate for the designated time. This technique ensured standardized volume *and* time exposure to the infusate. Animals in which the biliopancreatic duct did not accept the required amount of fluid at 30 mmHg (equivalent to 40 cmH$_2$O) within the designated time limit were excluded from further study (n = 13). The catheter was removed and the duodenal wall was closed with a 6–0 prolene suture and the abdomen with 4–0 nylon. The animals then were placed back in cages with minimal environmental stimuli.[12] Animals in groups 4 through 6 and 8 through 12 received a continuous intravenous infusion of cerulein at 5 μg/kg/hour (Farmitalia, Carlo Erba GmbH, 7800 Freiburg, Federal Republic of Germany) for 6 hours. Cerulein was reconstituted in normal saline such that the volume infused was 1 mL/hour. In saline controls (group 1), low-dose GDOC controls (groups 2 and 3), and high-dose GDOC group 7, the same volume of isotonic saline was used instead of cerulein. The combination of intraductal GDOC (10 mmol/L) and intravenous cerulein used in group 6 then was studied further with modifications of intraductal infusion volume and duration (modulation groups 8 and 9) and time of death after 24 hours (progression groups 10 through 12.).

Monitoring (Groups 1 Through 7)

Mean arterial blood pressure as well as central venous pressure and heart rate were continuously monitored (Becton-Dickinson, Electrodyne, Sharon, MA 02067). Hematocrit, arterial blood gases, serum amylase, and blood electrolytes (sodium, chloride, ionized calcium, and potassium) as well as glucose were measured at *baseline* and *6 hours* after the induction of pancreatitis. Blood gases, electrolytes, and glucose were measured using a STAT PRO 5 analyzer (NOVA Biomedical, Waltham, MA 02254). Osmolality, base excess, and bicarbonate concentration were calculated from the measured variables using the formulas described by the National Committee for Clinical Laboratory Standards (NCCLS)[13] and Tietz.[14] Serum amylase activity was determined using the colorimetric technique described by Bernfeld[15] and Warshaw.[16]

Histopathologic Analysis

The animals were killed by a lethal dose of pentobarbital (200 mg/kg intravenously [I.V.]) at the designated end points (6 and 24 hours) and rapidly bled through the indwelling arterial line. The entire pancreas was immediately removed and fixed in 10% formalin in anatomic orientation for histologic analysis. After dividing the organ into a duodenal and splenic part and embedding each in paraffin, one longitudinal section through each of the two parts was stained with hematoxylin and eosin. The total surface of the slides was scored by two blinded pathologists with expertise in pancreatic pathology (CC, KL) for six different variables determining severity of injury. The first 30 animals of the study were scored by both investigators. There was never more than 0.5 score point deviation in their judgment. Subsequent analysis therefore was performed by either pathologist 1 or 2. To detect small in-

TABLE 2. *Histopathologic Scoring Criteria (2 slides/animal)*

Edema	
0	Absent
0.5	Focal expansion of interlobar septae
1	Diffuse expansion of interlobar septae
1.5	Same as 1 + focal expansion of interlobular septae
2	Same as 1 + diffuse expansion of interlobular septae
2.5	Same as 2 + focal expansion of interacinar septae
3	Same as 2 + diffuse expansion of interacinar septae
3.5	Same as 3 + focal expansion of intercellular spaces
4.	Same as 3 + diffuse expansion of intercellular spaces
Acinar necrosis	
0	absent
0.5	Focal occurrence of 1–4 necrotic cells/HPF
1	Diffuse occurrence of 1–4 necrotic cells/HPF
1.5	Same as 1 + focal occurrence of 5–10 necrotic cells/HPF
2	Diffuse occurrence of 5–10 necrotic cells/HPF
2.5	Same as 2 + focal occurrence of 11–16 necrotic cells/HPF
3	Diffuse occurrence of 11–16 necrotic cells/HPF (foci of confluent necrosis)
3.5	Same as 3 + focal occurrence of >16 necrotic cells/HPF
4	>16 necrotic cells/HPF (Extensive confluent necrosis)
Hemorrhage and fat necrotis	
0	Absent
0.5	1 focus
1	2 foci
1.5	3 foci
2	4 foci
2.5	5 foci
3	6 foci
3.5	7 foci
4	≥ 8 foci
Inflammation and perivascular infiltrate	
0	0–1 intralobular or perivascular leukocytes/ HPF
0.5	2–5 intralobular or perivascular leukocytes/ HPF
1	6–10 intralobular or perivascular leukocytes/ HPF
1.5	11–15 intralobular or perivascular leukocytes/ HPF
2	16–20 intralobular or perivascular leukocytes/ HPF
2.5	21–25 intralobular or perivascular leukocytes/ HPF
3	26–30 intralobular or perivascular leukocytes/ HPF
3.5	>30 leukocytes/HPF or focal microabscesses
4	>35 leukocytes/HPF or confluent microabscesses

All data are presented as mean ± SEM. Continuous variables (MAP, etc.) were analyzed using the Kruskal and Wallis analysis of variance between groups (Proc NPAR1WAY, SAS Software, Cary, NC 27512). Because dynamic changes rather than absolute values are of interest, the analysis of all continuous variables was performed by calculating the difference between each time point and the baseline measurement. Categoric variables (histopathologic scores) were analyzed with the modified analysis of variance for discrete data (Proc CATMOD, SAS Software). A probability of type 1 experimental error ≤5% ($p \leq 0.05$) was considered acceptable for statistical significance.

HPF, high-power field.

crements in histopathologic severity, the standardized scoring system shown in Table 2 was applied.

Results

Initial Studies

Central Hemodynamics (Groups 1 Through 7). Within the 6-hour observation period, mean arterial pressure remained stable in all groups except high-dose GDOC group 7, which had significantly lower values than cerulein controls (4) and combination groups 5 and 6 (cerulein/GDOC 5 or 10 mmol/L) at 5 and 6 hours. Central venous pressure was constant in all groups. A pronounced increase in heart rate was found in combination group 6 (cerulein/GDOC 10) with significantly higher values at 6 hours than in saline controls (group 1) ($p < 0.04$) and cerulein controls (group 4) ($p < 0.01$) (Fig. 1). This tachycardia with constant central venous and mean arterial pressure is consistent with moderate hypovolemia in combination group 6 (cerulein/GDOC 10).

Gas Exchange (Groups 1 Through 7). Arterial oxygenation (Pa_{O_2}) showed an increase in combination group 6 (cerulein/GDOC 10) with higher values than all other groups ($p = 0.01$ to 0.04) (Fig. 1). Arterial carbon dioxide partial pressure (Pa_{CO_2}) decreased to an average of 32 mmHg in combination group 6, and was significantly lower than all other groups with the exception of low-dose GDOC control group 3 (10 mmol/L) and high-dose GDOC group 7 ($p = 0.01$ to 0.04) (Fig. 1). This finding in the presence of increased pH and unchanged base excess can be characterized as result of hyperventilation in combination group 6 (cerulein/GDOC 10).

Laboratory Parameters (Groups 1 Through 7). Serum amylase levels remained unchanged in saline controls and low-dose GDOC controls 2–3 (5 or 10 mmol/L). Highly significant increases were found in the groups receiving cerulein (groups 4 through 6) when compared with both low-dose GDOC controls (groups 2 and 3) and high-dose GDOC (group 7) ($p = 0.0001$ to 0.004). Ionized calcium levels decreased only in combination group 6 (cerulein/GDOC 10) and were lower than in low-dose GDOC control group 3 (10 mmol/L, $p < 0.007$) and cerulein controls 4 ($p < 0.04$) (Fig. 1). The hematocrit in combination group 6 (cerulein/GDOC 10) was significantly higher than in saline controls ($p < 0.02$), and low-dose GDOC control groups 2 (5 mmol/L, $p < 0.007$) and 3 (10 mmol/L, $p < 0.002$) (Fig. 1). Blood leukocyte counts increased in combination groups 5 and 6 (cerulein/GDOC 5 or 10

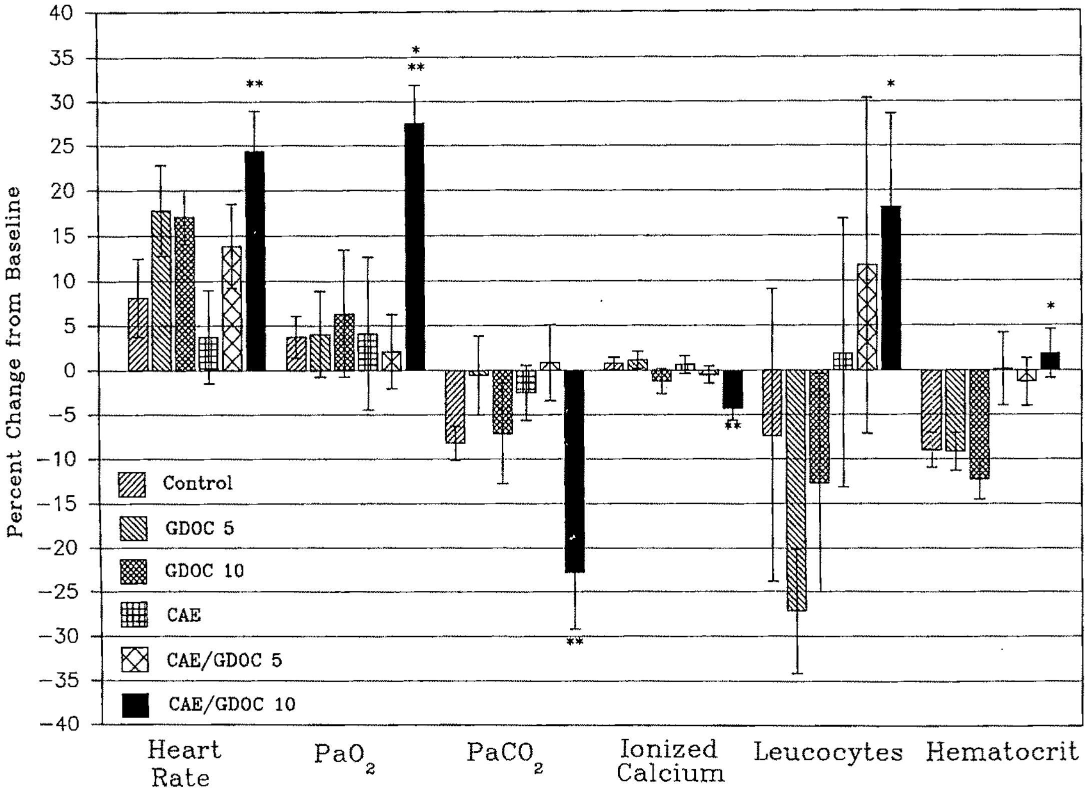

FIG. 1. Hemodynamic and laboratory parameters that showed significant differences between groups. Asterisks indicate significant differences between combination group 6 (cerulein/GDOC 10) and low-dose GDOC control groups 2 and 3 (5 or 10 mmol/L) (*) or cerulein control group 4 (**). All intraductal infusions of saline or GDOC were at a low pressure of 30 mmHg (40 cm H_2O) and a volume of 0.1 to 0.15 mL over 1.5 min.

mmol/L) (Fig. 1). Serum sodium, chloride, potassium, and glucose concentrations as well as osmolality remained unchanged during the experiments. These results indicate increased hyperamylasemia, hypocalcemia, hemoconcentration, and leukocytosis in combination group 6 (cerulein/GDOC 10) compared with saline, cerulein, and low-dose GDOC controls.

Histopathology

Saline Controls. The achieved increments in histopathologic scores are depicted in Figure 2. All pancreatitis groups had significantly higher mean inflammatory scores for all variables than did saline controls ($p = 0.0001$ to 0.04). Apart from minimal focal edema, saline controls showed entirely normal acinar architecture (Figure 3).

Cerulein or Low-dose GDOC Alone. Low-dose GDOC control groups 2 and 3 (5 or 10 mmol/L) demonstrated only mild edema, little acinar necrosis and inflammation (Fig. 4), occasionally associated with some foci of hemorrhage and fat necrosis. The main histopathologic finding in cerulein controls (group 4) was moderate edema and occasional single-cell necrosis with only few leukocytes, frequently with moderate fat necrosis, but no hemorrhage.

Cerulein Combined With Low-dose GDOC. A stepwise increase in mean scores across groups was found in low-dose GDOC controls (groups 2 and 3), cerulein controls (group 4), and in the combination groups 5 and 6 (cerulein/GDOC 5 or 10 mmol/L), with significant differences between low-dose GDOC controls (groups 2 and 3) and cerulein controls (group 4) compared with combination group 6 (cerulein/GDOC 10) for the key variables determining inflammatory severity (*edema* $p < 0.0005$, *acinar necrosis* $p < 0.01$, *inflammation* $p < 0.006$). Intrapancreatic *hemorrhage* and *perivascular inflammation* also were increased significantly in combination group 6 (cerulein/GDOC 10) compared with cerulein controls (group 4) ($p < 0.01$, $p < 0.0001$). In combination group 6 (cerulein/GDOC 10), the histopathologic appearance of pronounced edema, marked interstitial leukocyte infiltration, intrapancreatic hemorrhage (Fig. 5), and fat necrosis was similar to the histopathology of moderately severe human pancreatitis. Most importantly, moderate scores for *acinar necrosis* were constant findings *only* in combination groups 5 and 6 (cerulein/GDOC 5 or 10 mmol/L) with homogeneous distribution (Figure 6).

High-dose GDOC Alone. In contrast to combination

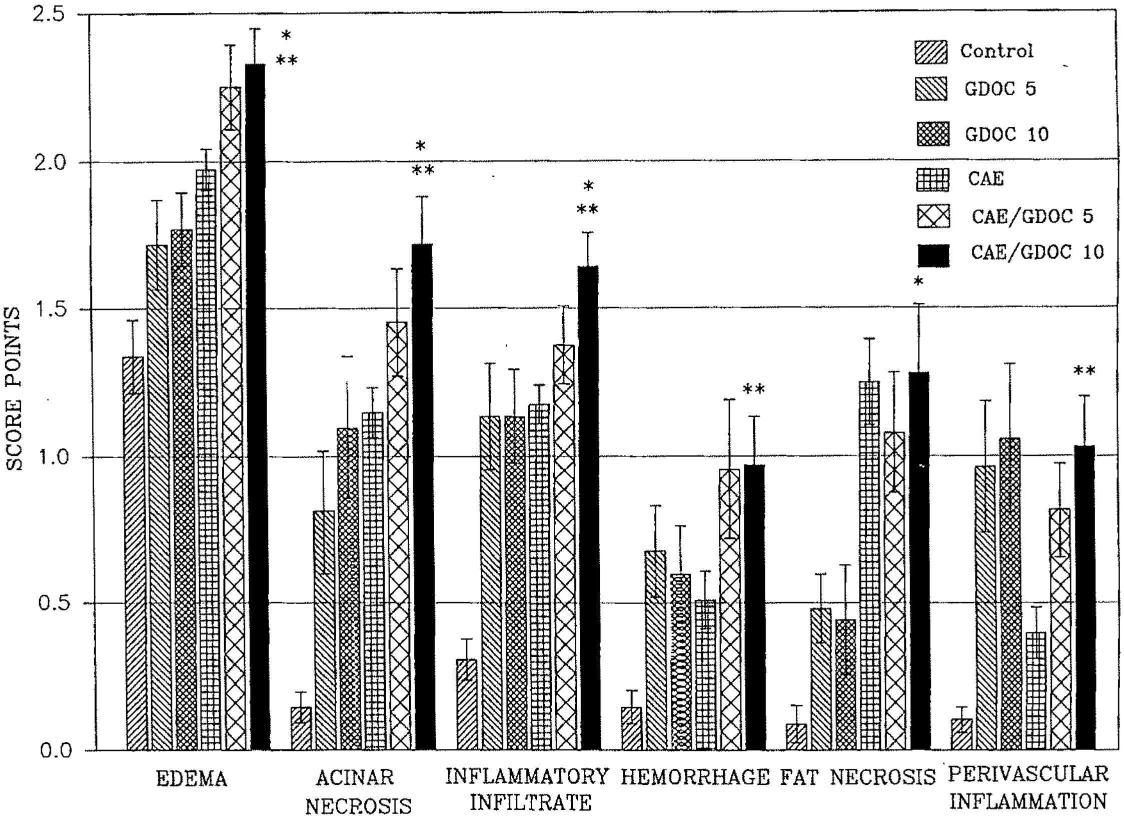

FIG. 2. Histopathologic findings at 6 hr. Asterisks indicate significantly higher values in combination group 6 (cerulein/GDOC 10) compared with low-dose GDOC control groups 2 and 3 (5 or 10 mmol/L) (*) or cerulein control groups 4 (**). All intraductal infusions were at a pressure of 30 mmHg (40 cm H_2O) and a volume of 0.1 to 0.15 mL over 1.5 min. Note the stepwise increase in mean scores for edema, acinar necrosis, and inflammation.

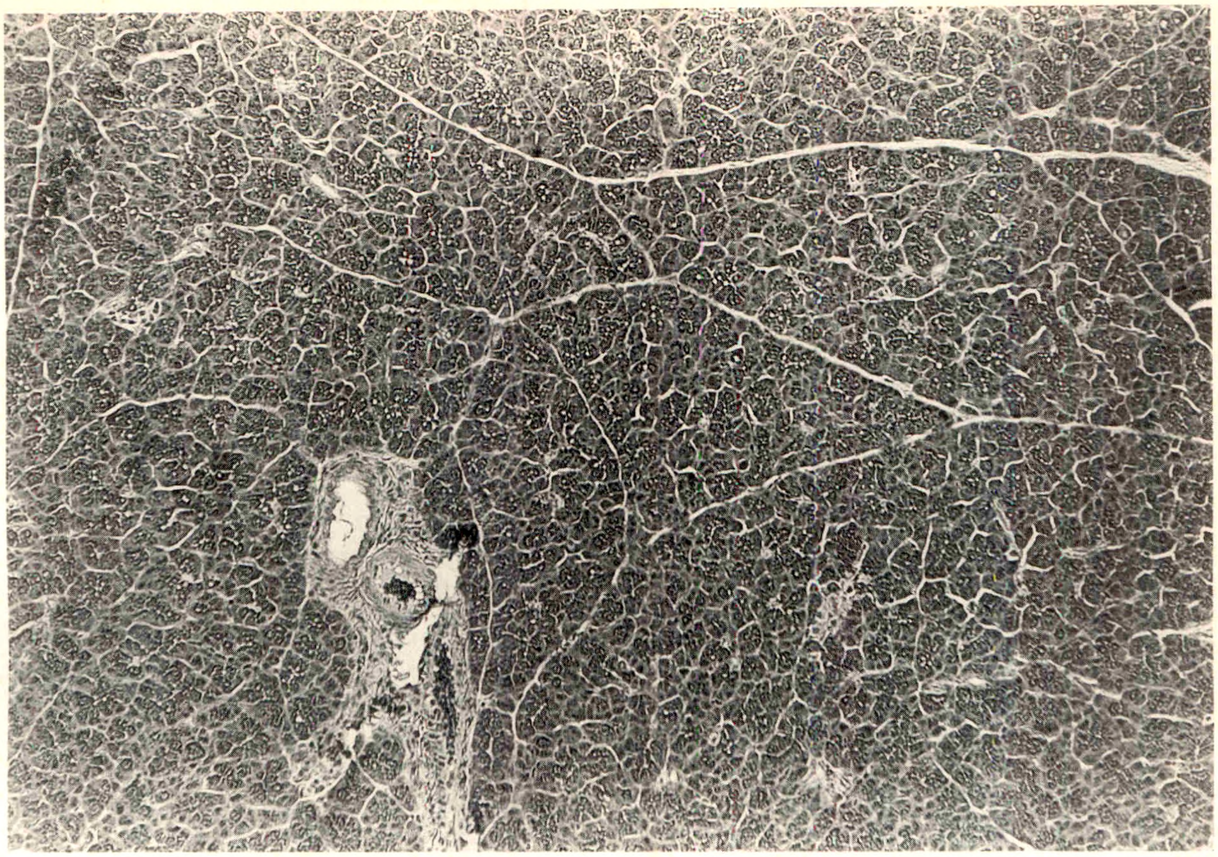

FIG. 3. Pancreas in a control animal 6 hr after intraductal and intravenous saline infusion. The glandular architecture is entirely normal (H & E, ×80).

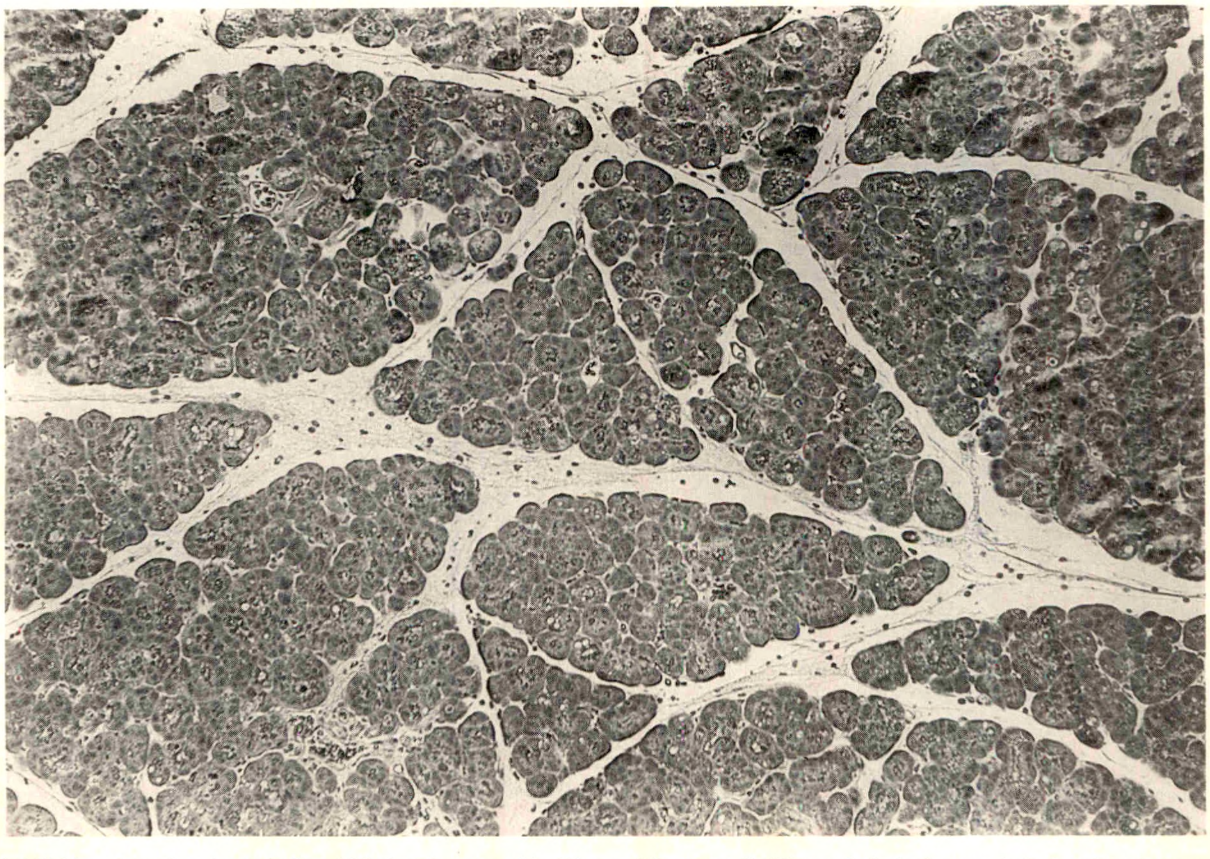

FIG. 4. Mild low-dose glycodeoxycholic acid-induced pancreatitis (10 mmol/L, group 3). Histopathologic features include mild edema, minimal necrosis, and inflammatory infiltration (H & E, ×80).

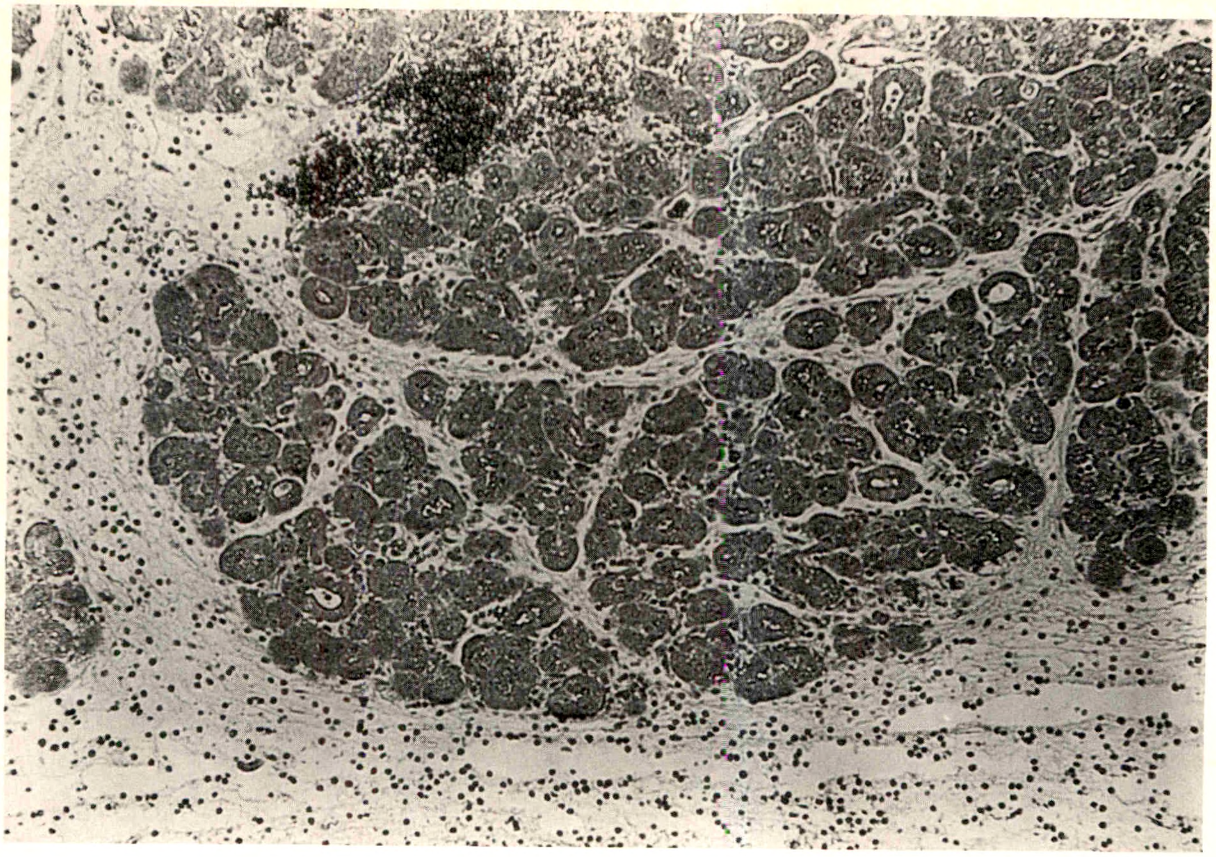

FIG. 5. Moderately severe pancreatitis after combined induction with intravenous cerulein and low pressure- (30 mmHg), volume- (0.1–0.15 mL), and time-controlled (1.5 min) intraductal glycodeoxycholic acid infusion at 10 mmol/L (6). Moderate to severe edema, substantial inflammatory infiltrate, and moderate hemorrhage as well as significant cell necrosis are the principal features (H & E, ×80).

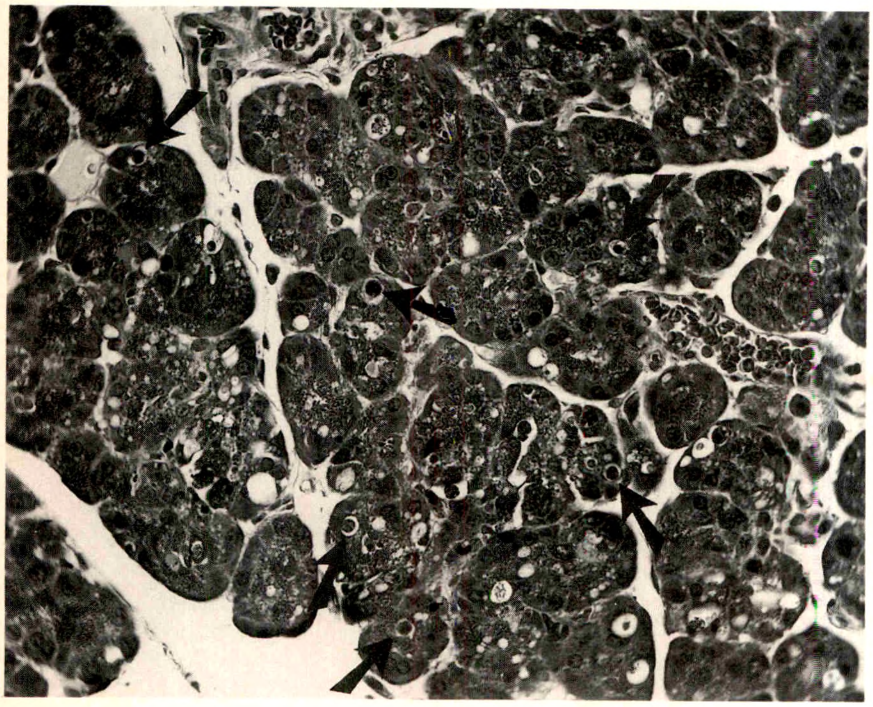

FIG. 6. High-power field of pancreatitis in a rat receiving the combination of intravenous cerulein and low pressure- (30 mmHg), volume- (0.1–0.15 mL), and time-controlled (1.5 min) intraductal glycodeoxycholic acid infusion at 10 mmol/L (group 6). At 6 hr there is a consistent finding of single cell necrosis with homogeneous distribution of the lesions (H & E, ×313). The arrows indicate necrotic acinar cells with a pyknotic nucleus in the center, partial karyorhexis, and a bright border due to cytoplasmatic shrinkage and cell degeneration.

group 6 (cerulein/GDOC 10), high-dose GDOC group 7 (34 mmol/L) caused severe pancreatitis. Acinar necrosis was catastrophic and involved entire lobules, with extremely patchy distribution. Intense granulocyte infiltration was uniformly present (Fig. 7) and frequently accompanied by widespread hemorrhage.

Histopathologic Homogeneity. The mean differences between the scores for each variable in the duodenal and the splenic portion of the pancreas are depicted in Figure 8. In addition to the extremely focal panlobular necrosis in the high-dose GDOC group (7), the injury was virtually confined to the head of the pancreas, whereas the splenic portion was unaffected. This is reflected by distinctly higher mean differences between duodenal and splenic scores for each variable. In contrast, homogeneity of injury in combination group 6 (cerulein/GDOC 10) was demonstrated by significantly lower head/tail differences than that of all other pancreatitis groups except cerulein controls (4) and combination group 5 (cerulein/GDOC 5) for edema ($p = 0.0001$ to 0.05), acinar necrosis ($p = 0.0001$ to 0.03), and inflammation ($p = 0.0007$ to 0.02). These results demonstrate that using the combination of intravenous cerulein and intraductal low-dose GDOC affects the duodenal and splenic portion of the pancreas equally.

Further Studies

Modulating Histopathologic Severity. The ability to adjust the severity of pancreatic inflammation offers potential advantages for the study of its therapy. We therefore evaluated the effect of prolonging the duration and increasing the volume of intraductal infusion of low-dose GDOC at 10 mmol/L in combination with intravenous cerulein (modulation groups 8 and 9). The results are depicted in Figure 9. The inflammatory severity after *6 hours* was significantly increased when the intraductal infusion was lengthened from 1.5 to 2.5 or 10 minutes and the infused volume was increased from 0.1 to 0.15 mL to 0.2 to 0.25 or 0.5 to 0.55 mL. Highly significant differences were found between combination group 6 (1.5 minutes/0.1 to 0.15 mL) compared with modulation groups 8 (2.5 minutes/0.2 to 0.25 mL) and 9 (10 minutes/0.5 to 0.55 mL) for acinar necrosis ($p < 0.006$), inflammation ($p < 0.001$), hemorrhage ($p < 0.0009$) and perivascular in-

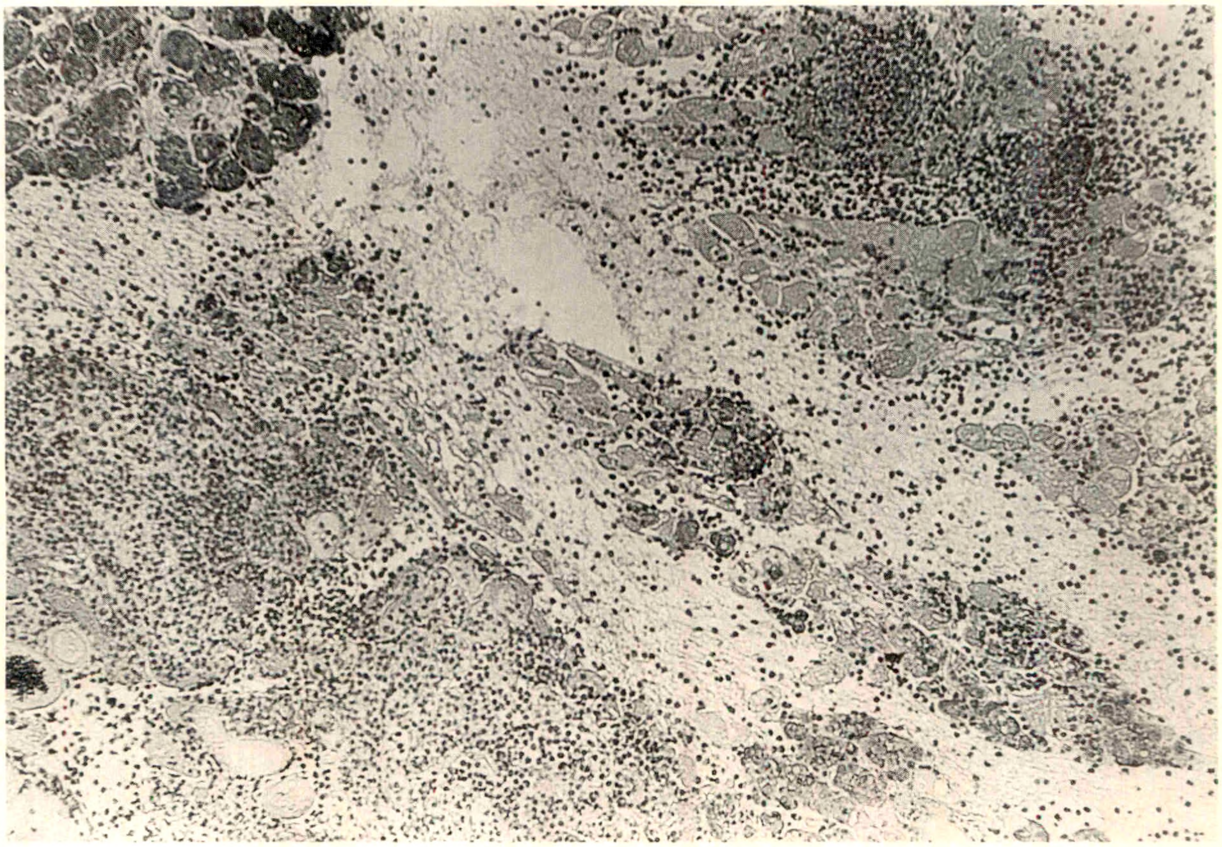

FIG. 7. Catastrophic pancreatitis 6 hr after intraductal high-dose (34 mmol/L, group 7) glycodeoxycholic acid infusion. There are numerous entirely destroyed lobules with extreme leukocytic infiltration and frequently widespread hemorrhage (not shown). The histopathologic aspect reflects the immediate cytolytic effect of bile acid at high concentrations (H & E, ×80).

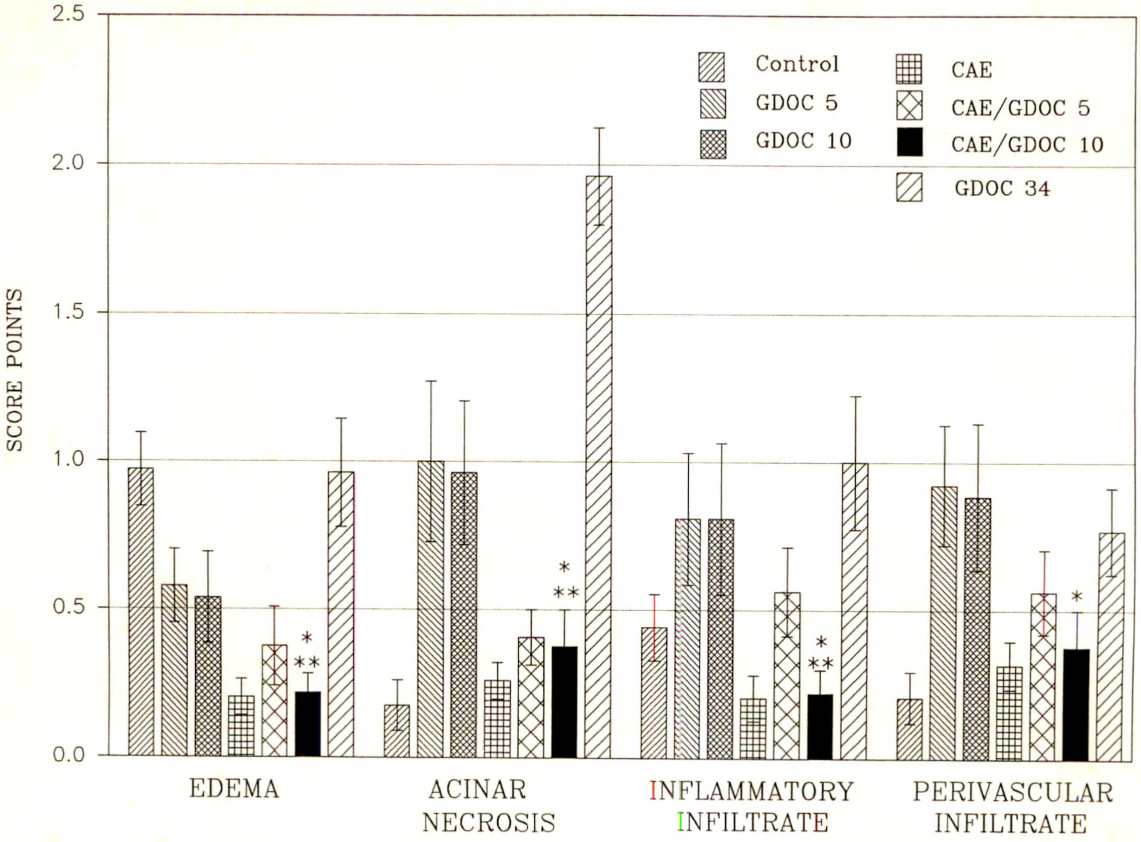

FIG. 8. Homogeneity of pancreatitis as reflected by the mean differences between scores for duodenal and splenic portions of the pancreas for the important histopathologic variables under investigation. Asterisks indicate significantly lower values in combination group 6 (cerulein/GDOC 10) compared with high-dose GDOC group 7 (34 mmol/L) (*) or low-dose GDOC control groups 2 and 3 (5 or 10 mmol/L) (**). All intraductal infusions were at a pressure of 30 mmHg (40 cmH$_2$O) and a volume of 0.1 to 0.15 mL over 1.5 min.

filtrate ($p < 0.02$). All histopathologic variables under investigation were highly significantly elevated when comparing combination group 6 and modulation group 9 ($p = 0.0001$ to 0.006).

24-Hour Mortality. To evaluate the mortality of the induced inflammation, we studied three additional groups (groups 10 through 12) employing identical induction techniques as in combination group 6 and modulation groups 8 and 9, but with prolonged observation for *24 hours.* When combining intravenous cerulein with intraductal low-dose GDOC over 1.5 minutes at a volume of 0.10 to 0.15 mL in group 10, only one of 17 animals died (6%), compared with three of 15 animals (20%) in group 11 when intraductal low-dose GDOC was given over 2.5 minutes at a volume of 0.2 to 0.25 mL. Finally, five of 12 animals (42%) died in group 12 when low-dose intraductal GDOC was infused over 10 minutes at a volume of 0.5 to 0.55 mL. These results represent a threefold and sixfold increase in mortality rate, respectively. The mortality rate differences correlate with the magnitude of the induction stimulus and reflect increasing histopathologic severity found in the three modulation groups.

Time Course. The results of histopathologic analysis after 24 hours of the cumulative progression and the progression of the individual variables are depicted in Figures 10 and 11, respectively. A pronounced increase in histopathologic scores was found, with significant differences between groups 6 (6 hours) and 10 (24 hours) for acinar necrosis ($p < 0.02$), inflammation ($p < 0.0001$), hemorrhage ($p < 0.005$), fat necrosis ($p < 0.0001$), and perivascular inflammation ($p < 0.0001$). Significant progression between groups 8 (6 hours) and 11 (24 hours) also was present for acinar necrosis ($p < 0.04$), inflammation ($p < 0.002$), and fat necrosis ($p < 0.0001$). In group 12 (24 hours), significant increases in severity of inflammation compared with group 9 (6 hours) were found for inflammation ($p < 0.01$) and fat necrosis ($p < 0.04$). These findings indicate a substantial increase of histopathologic severity in the interval from 6 to 24 hours after induction.

Discussion

Approximately 20,000 cases of acute pancreatitis occur annually in the United States and Britain.[17,18] With the

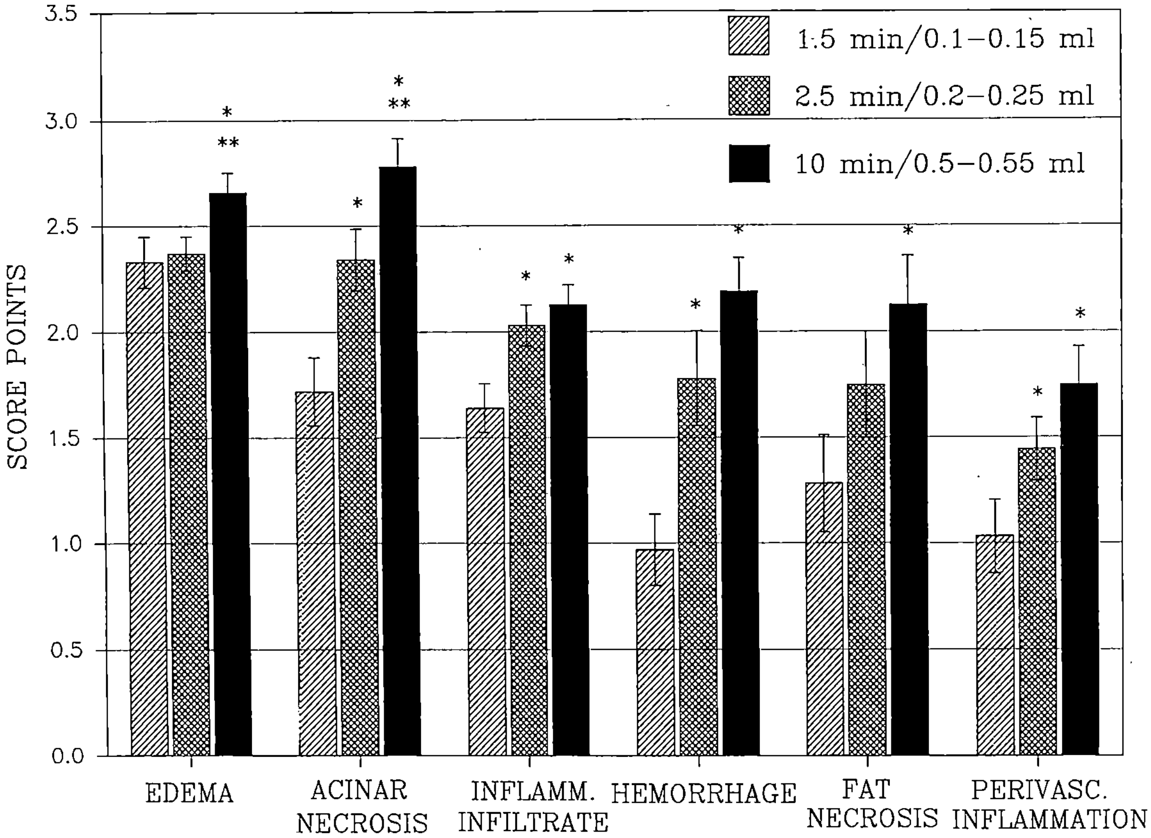

FIG. 9. Modulation of inflammatory severity 6 hr after combined induction with intravenous cerulein and intraductal glycodeoxycholic acid (10 mmol/L) infusion by prolongation of infusion time and increased volume. Asterisks indicate significant group differences compared with combination group 6 (1.5 min/0.1–0.15 mL) (*) or combination group 6 and modulation group 8 (2.5 min/0.2–0.25 mL) (**).

disease involving severe necrotizing injury, mortality rates up to 40% may occur.[4] Factors that influence the severity of an attack are largely unknown, but there may be a period early in the evolution of this disease that determines whether the reversible phase of pancreatitis converts to irreversible tissue injury and acinar necrosis.[19] Therapeutic interventions can have the greatest impact on the fate of the patient before such a turning point. In this study, we sought to design a better model of pancreatitis suitable to investigate innovative therapy. The new model should produce pancreatic injury that is substantial enough to require therapy, but not so severe that initiated treatment is too little too late. Our results show that such a model can be readily produced by combining minimal intraductal bile acid exposure and supramaximal pancreatic stimulation. Its severity is progressive over time, can be easily modulated, and its morphology closely resembles that of human pancreatitis.

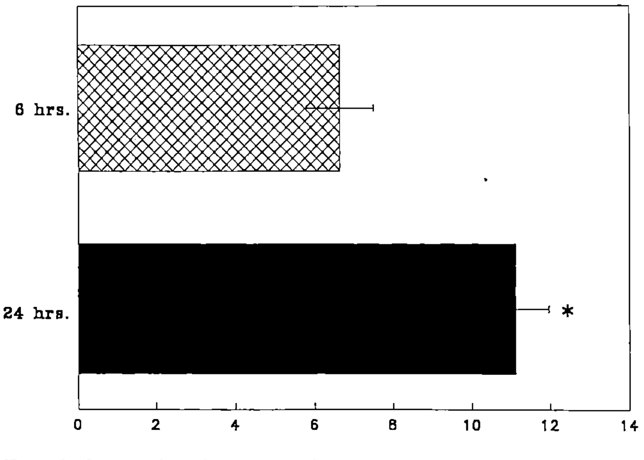

FIG. 10. Cumulative histopathologic progression for acinar necrosis, inflammation, hemorrhage, fat necrosis, and perivascular infiltrate 6 and 24 hr after intraductal low-dose glycodeoxycholic acid and intravenous cerulein (group 6 *vs.* group 10).

Advantages of some previous experimental models (including the cerulein and CDE diet-induced pancreatitis) are that the pancreatitis can be induced by noninvasive techniques,[20] and that the inflammatory lesions in these models are homogeneously distributed. These animal preparations, however, either cause only minimal necrosis in the rat[7] or else lead to severe necrotizing injury, which develops over a variable time range and can be produced only in young female mice.[11] Although these models have

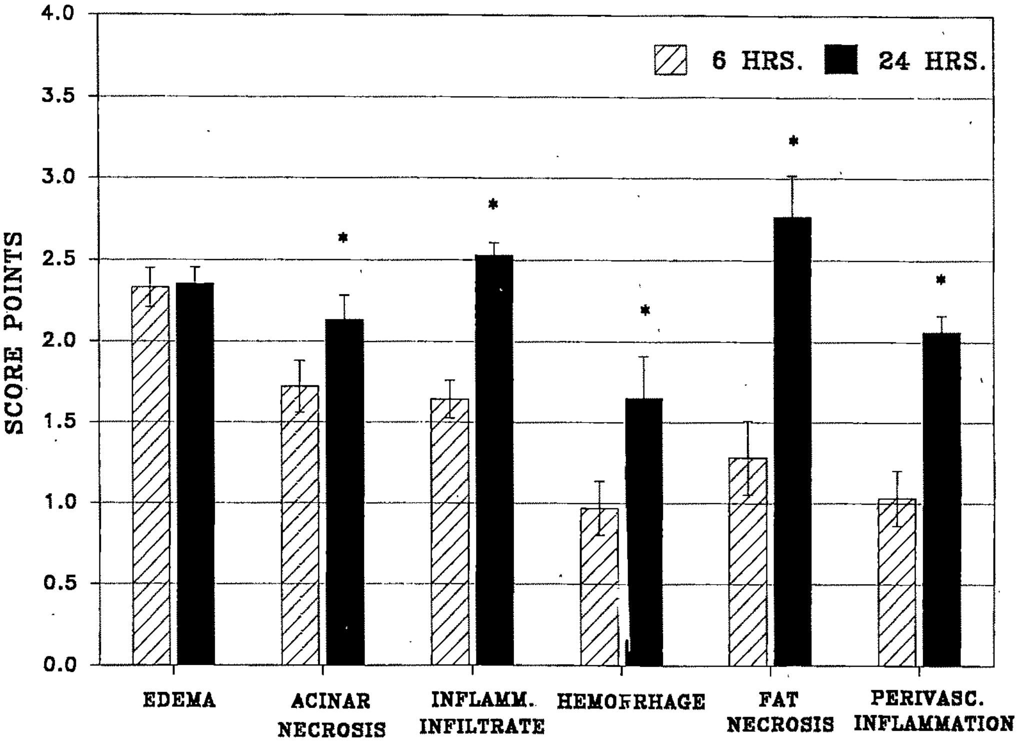

FIG. 11. Comparison of individual histopathologic features at 6 and 24 hr. Asterisk (*) indicates significant difference between groups with identical induction regimens (group 6 *vs.* group 10).

been helpful in exploring pathophysiologic aspects of acute pancreatitis, their suitability to investigate new therapeutic strategies is limited. Traditional invasive reflux models, however, cause rapid severe necrosis—against which there can be no protection—and heterogeneous injury indicative of nonphysiologic localized duct trauma.[8–10,21–23] Many investigators disregarded the need for control of infusion pressure as well as of volume and time of intraductal exposure, but instead have used uncontrolled manual injection or infusion at unphysiologic pressures as high as 600 mmHg, which produced severe barotrauma.[24–26] Moreover, as the various bile acids have very different toxicities in pancreatic tissue, it is essential to use only standardized bile acid solutions.[27] Finally, the concentration of the infused bile salt also greatly influences the homogeneity of the inflammatory lesions. Aho et al.[8,9] suggested that the detergent effect of taurocholate at high concentrations immediately breaks down the integrity of the proximal biliopancreatic duct; bile salts leak into the local interstitium and fail to reach acinar cells at the periphery of the duct system. This concept was confirmed in our study. The marked cytolytic effect of GDOC (34 mmol/L) on the duct mucosa caused immediate, frequently macroscopically visible, obstruction by edema and diffuse hemorrhage in and around the ductal system in the head of the pancreas. The importance of this observation is supported histopathologically by the enormous head/tail difference for acinar necrosis (massive in the head, absent in the tail) and the other histopathologic variables when infusing GDOC at this concentration. High concentrations of bile acids, therefore, have limited suitability for the induction of experimental pancreatitis because extensive acinar necrosis is too rapidly established and because the resulting lesions demonstrate substantial heterogeneity.

An advantage of very low concentrations of GDOC (5 or 10 mmol/L) is that they do not elicit this immediate detergent effect[27] and allow for the further dispersion of the infusate out to the periphery of the pancreas, but their disadvantage is that they produce only minimal morphologic evidence of pancreatitis with no death. Similarly, cerulein also results in only mild self-limited pancreatitis in the rat. We hypothesized that acinar cells previously exposed to controlled intraductal infusion of low-dose bile salt might be more likely to be injured by supramaximal secretory stimulation. Our results show that the combination of both agents produces pancreatitis exceeding that induced by either component alone and provides an excellent model of intermediate severity. Similarly, Evander et al.[28] found that cerulein potentiated the gross macroscopic manifestations of uncontrolled manual injections of sodium taurocholate in combination with active trypsin. Although supramaximal stimulation such as that produced by cerulein may not occur under physiologic conditions, some cases of human pancreatitis have been attributed to the interaction of obstructed pancreatic outflow and simultaneous hyperstimulation.[29,30]

Several alternative approaches to transform mild edematous pancreatitis into a more severe form have been described. Niederau et al.[31] demonstrated that mild cerulein pancreatitis in mice can develop into a necrotizing form by repeated injections of supramaximal cerulein doses, but these findings were never confirmed for the rat, and more importantly, this form of pancreatitis bears no mortality rate. Yamaguchi et al.[12] showed that intensive stress over several hours (water immersion/23 C) can transform cerulein pancreatitis into hemorrhagic disease. In that study, however, the degree of acinar necrosis in the cerulein/stress group was not different from cerulein pancreatitis, and no deaths occurred. It is also not clear whether the development of pancreatic hemorrhage in this model was caused by hypothermia. Spormann et al.[32] demonstrated that variable ischemia periods (clamping of pancreas-supplying arteries) superimposed on pancreatic duct ligation could produce more severe pancreatitis, but because of individual variations in pancreatic blood supply and different ischemia tolerance, this model has a variable outcome.

Aside from the fact that it produces pancreatitis of intermediate severity with mortality rates between 6% and 42% at 24 hours in the variations tested, the model herein described has several attractive features. First, as demonstrated by the small differences between the histopathologic scores of the duodenal and splenic portions, the pancreatitis produced is homogeneously distributed through the gland and is therefore easily and reliably scored for comparisons; second, the progression of histopathologic injury over at least 24 hours makes the model particularly attractive for therapeutic studies; and third, the intensity of the initial intraductal irritation (time and volume of bile acid infusion) can be used to modulate the severity of pancreatitis as assessed by histopathology and mortality data. Neither cerulein nor GDOC at 5 or 10 mmol/L by themselves were able to reproduce these features and did not cause more than mild inflammatory changes. Substantial cell necrosis was seen to an important degree only when cerulein and GDOC at 10 mmol/L were combined. The greater tachycardia, hyperventilation, hemoconcentration, leukocytosis, and hypocalcemia in the combination group compared with low-dose GDOC or cerulein alone provides physiologic confirmation of the histopathologic increase in severity of pancreatitis.

In summary, we have developed and characterized a much improved model of acute pancreatitis using the combined action of very low concentrations of intraductal glycodeoxycholic acid and intravenous pancreatic secretory stimulation with cerulein. Its attractive features are a moderate rate of onset, homogeneous injury of intermediate severity, the potential for modulating the severity, and the progression of pancreatic cell injury over at least 24 hours. This model, therefore, appears particularly suitable to study innovative treatment designed at limiting the extension of ongoing necrosis in acute experimental pancreatitis.

Acknowledgment

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Long-term Results After Colectomy and Endorectal Ileal Pullthrough Procedure in Children

ERIC W. FONKALSRUD, M.D., and NANCY LOAR, R.N.

Since 1987, 67 children with ulcerative colitis, 14 with colonic polyposis, and one with Hirschsprung's disease have undergone colectomy and endorectal ileal pullthrough procedures (ERP). Seventy-six children had a lateral ileal reservoir and six had a straight pullthrough. Seventy-seven patients had a diverting ileostomy for 4 months; five polyposis patients underwent ERP without ileostomy. Forty-three (52%) developed complications, including ileoanal stenosis with reservoir outlet obstruction (14), elongated ileal spout (2), elongated ileal reservoir > 15 cm (4), and a combination of outflow obstruction, reservoir enlargement causing stasis (14), and intestinal obstruction causing obstruction (10). Thirty-two children required reoperation. Sixty per cent of complications occurred in the first 30 patients. Only three of the last 40 patients had reoperation. There were no deaths. Four children (two with Crohn's disease) returned to a permanent ileostomy (4.9%); 10 had a temporary ileostomy. Five straight pullthroughs were converted to a reservoir because of stool frequency; 19 underwent reservoir reconstruction because of stasis. Seventy-five children (91.5%) are currently progressing very well. Features for optimal function include a short rectal muscle cuff, a short reservoir and spout, and aggressive correction of rectal strictures. The ERP is a desirable option to proctocolectomy and ileostomy for children with colitis or polyposis.

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DURING THE PAST decade, colectomy with mucosal proctectomy and endorectal ileal pullthrough (ERP) has been used with increasing frequency for the definitive surgical treatment of ulcerative colitis (UC) that is refractory to medical therapy, and for patients with familial polyposis. This procedure cures the disease and obviates the unpleasant and cumbersome features of a permanent ileostomy and the morbidity of proctectomy. After the report by Martin and associates in 1977,[1] indicating a good outcome in 15 of 17 children with a straight ERP after colectomy and mucosal proctectomy, the procedure has been used extensively in children, but has undergone many modifications. The procedure is now generally accepted as the most favorable option for the surgical treatment of UC and familial polyposis in childhood.[2-5]

The ERP is a modification of the rectal mucosal stripping procedure described by Soave in 1965[6] for the treatment of Hirschsprung's disease. Removal of the entire rectal mucosa down to the dentate line has been shown not to interfere appreciably with anorectal sphincter function or the ability to discriminate between gas and liquid or solid contents. The straight ERP without reservoir has been recommended for children by a few surgeons.[7] Long-term follow-up, however, has indicated that most of these patients experience persistent frequency and urgency, and in some cases incontinence, which interferes greatly with the performance of daily activities. The majority of surgeons performing the endorectal ileal pullthrough operations, therefore, have used an ileal reservoir above the ileonal anastomosis to reduce peristalsis in the distal ileum and to provide an area for fecal storage. Regardless of the type of reservoir technique performed, as long as the lower 4 cm of the rectal muscle is not damaged, the anal sphincter resting pressure and the anal sphincter squeeze pressure will be close to normal within 6 weeks.

Children with chronic UC often present with many of the same signs and symptoms as adults, although frequently more acute and severe. Because of the metabolic demands of growth and maturation, children may suffer additional difficulties such as growth retardation, delayed puberty, psychosocial disturbances, and profound malnutrition. Because most reports concerned with the ERP during the past several years have been concerned with adult patients, the present report was undertaken to summarize our clinical experience in the treatment of 82 children under 19 years of age with the ERP during a 14-year period.

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Materials and Methods

During the period from 1977 through 1991, 67 children with UC, 14 with familial polyposis coli, and one with Hirschsprung's disease underwent colectomy and the ERP at UCLA Medical Center. There were 44 girls and 38 boys, ranging in age from 6 to 18 years (mean, 14.6 years). Six children were under the age of 10 years at the time of operation and 21 were between 10 and 14 years. During the same period, an additional 258 patients 19 years of age and older with UC or polyposis underwent colectomy and ERP. Seventy-six children had a lateral ileal reservoir (LR), and six had a straight pullthrough without reservoir.

The duration of the colitis ranged from 3 months to 9 years (mean, 3.6 years). One or more members of the immediate family constellation from 11 of the children with UC (16%) had UC or Crohn's disease. Symptoms of UC were apparent before the age of 10 years in 12 patients (18%). For most children, the symptoms began insidiously with persistent diarrhea followed by the appearance of blood, mucus, and pus in the stools. Cramping lower abdominal pain, low-grade fever, and tenesmus were common during flare-ups of the colitis. Anorexia, weight loss, lethargy, and growth retardation were present in most children who had persistently active disease for more than 1 year. Several children had a notable delay in bone age, and others showed delayed sexual maturation, with late onset of menses and breast development in females, and delayed growth of testes and genitalia in males. External hemorrhoids were present in 24 children, but anal sinuses or fissures were present in only four patients.

Six children with UC had acute severe rectal bleeding, most within 6 months of the onset of the disease, which necessitated very urgent colectomy. Three children developed an acute fulminating exacerbation of the colitis with abdominal cramps, severe diarrhea, and dehydration that was unresponsive to high-dose steroids and other medications, and necessitated emergency colectomy. Twenty children (30%) had received one or more blood transfusions before operation.

Most of the children expressed feelings of frustration and progressive disinterest in participating in social and physical activities. More than half the children were appreciably behind in scholastic work and 14 had used home tutors on a long-term basis.

Thirty-four children with UC (51%) had arthralgias involving knees, ankles, spine, or wrists, and several showed evidence of osteoporosis. Six patients had nephrolithiasis (9%). Several children had aphthous stomatitis, and a few had erythema nodosum or mild uveitis.

Each of the 14 children with polyposis had the disease established during a screening study after another member of the immediate family was found to have diffuse colonic polyposis. One parent from seven of the children had carcinoma. Eleven of the children had another sibling with polyposis. Ten patients were asymptomatic, and four had occasional mild rectal bleeding or recurrent diarrhea. Two children had Gardner's syndrome.

At the time of operation, each of the 67 children with UC were receiving high-dose prednisone therapy. Nineteen of the children had received immunosuppressive therapy including 6-mercaptopurine, azathioprine, or cyclosporine. Eleven patients experienced severe growth retardation and were below the 15th percentile for height. Three children with protracted symptoms of UC extending more than 4 years who had received extensive medical therapy were considered unsuitable for the ERP operation because of marked obesity related to steroid use combined with a history of multiple systemic infections, presumably related to immunosuppressive therapy. Eleven girls and two boys developed large broad permanent striae over the thighs, hips, abdomen, and chest within 6 weeks after initiation of steroid therapy. Eighteen children had received one or more courses of total parenteral nutrition (TPN) and bowel rest before operation.

All children with colitis had normal small bowel roentgenographic studies preoperatively, although the radiographic contrast enema showed abnormal features in all patients on whom it was performed. Eighteen of the children had pancolitis, and the remainder had disease involving the rectum and left and transverse colon. Stool cultures showed no pathogens in any of the children. Mucosal biopsy was performed on all patients with colitis at an early stage to establish the diagnosis and to exclude those patients with Crohn's disease. Four children had an indeterminate type of colitis on mucosal biopsy, which subsequently proved to be Crohn's disease in two patients more than 1 year after colectomy and ERP had been performed.

Selection of children to undergo colectomy and ERP was made only after extensive medical therapy, and after the surgical options were discussed in detail with the patient, parents, and pediatrician. Most children spoke to other patients of the same sex and similar age who had undergone the operation previously to alleviate fears and to add support to the decision for operation. Corticosteroid therapy was maintained to avoid an acute flare-up before operation. Cleansing enemas were avoided for the same reason. Oral antibiotics (neomycin and erythromycin) were given for 18 hours before operation, and intravenous antibiotics (gentamicin and Cleocin [Upjohn, Kalamazoo, MI]) were initiated 4 hours preoperatively.

Operative Technique

In 1980, we reported our clinical experience with a lateral isoperistaltic ileal reservoir for patients with UC and polyposis[8]; this procedure has been modified during the ensuing years. The technique used for most children in the present study entails dividing the ileum within 1 cm of the ileocecal valve and mobilizing the mesentery up to the origin of the superior mesenteric artery to provide suitable length for the ileum to reach the anus without tension. It is rare for UC in children to extend into the distal ileum. The colon with omentum is removed down to the pelvis. The peritoneal reflection is incised circumferentially, and the rectum is mobilized with cautery dissection down to within 4 cm from the dentate line, where the full thickness of rectum is divided. The anus is dilated and a circumferential incision is made through the mucosa at the dentate line. The mucosa is elevated from the underlying muscularis with scissors and cautery, taking care to remove all mucosa. Thorough hemostasis is achieved.

The ileum is transected approximately 12 cm from the end, preserving the vascular supply to the distal segment. The proximal ileum is advanced to a position adjacent to the distal segment, and a lateral isoperistaltic anastomosis is performed between the antimesenteric sides of each using the general intestinal anastomosis (GIA) stapling device (Fig. 1). The upper end of the reservoir is closed with staples; however, the lower end is closed with a running inverting suture of 3–0 Maxon (Ethicon, Somerville, NJ). A second layer of interrupted absorbable suture is placed circumferentially around the entire reservoir anastomosis. A spout of less than 1 cm extends between the distal end of the reservoir and the open end of the ileum. The ileal reservoir is brought through the pelvis and rectal muscle canal such that the end of the ileum extends to the anus (Fig. 2). The ileal spout is sutured to the anoderm and underlying muscularis circumferentially with interrupted absorbable stitches. The ileum is transected approximately 10 cm above the upper end of the ileal reservoir, and the proximal end of the divided ileum is fashioned into an end ileostomy stoma. The pelvis is drained transabdominally for 4 days.

Intravenous steroids are tapered down rapidly after operation and oral prednisone is discontinued within 3 weeks. Most children were discharged from the hospital by the seventh postoperative day. A Gastrografin (Squibb, Princeton, NJ) enema was performed within 3 months to assure that the ileal reservoir had healed securely without leaks or sinus tracts. Most children resumed full physical activities within 3 weeks.

Each of the 67 children with UC, nine of those with polyposis, and the one with Hirschsprung's disease had a protecting ileostomy for approximately 4 months. Five children with colonic polyposis had the entire ERP performed in one stage without protecting ileostomy. Eight of the children with UC had a previous colectomy, ileostomy, and Hartmann rectal pouch performed at another hospital. The 17-year-old boy with Hirschsprung's disease had four previous pullthrough operations performed at other hospitals during previous years and had an ileostomy and modified rectal Hartmann pouch before the ERP procedure.

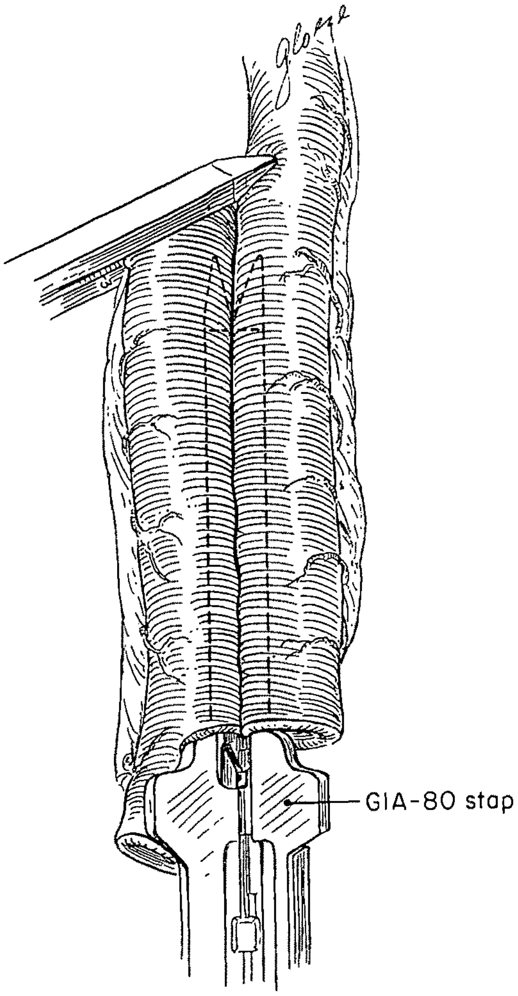

FIG. 1. Distal ileum is divided approximately 12 cm from the end, preserving the blood supply. Antimesenteric borders are approximated, and a small incision is made in the lower segment 1 cm from the end. A long anastomosis is constructed with the GIA stapler. The upper end of the lower segment is stapled. The lower end of the reservoir is closed with a continuous inverting suture of Maxon, leaving a spout of 1 cm or less.

Approximately 4 months after the first operation, each child was rehospitalized for approximately 6 days for ileostomy closure. Postoperatively, metronidazole was given for 6 to 8 weeks, and slight dietary modification was advised, minimizing only the intake of chocolate, vinegar, and spicy foods. Medications to reduce peristaltic activity and bulking agents were rarely necessary. The ileoanal anastomosis was stretched at the time of ileostomy closure and then dilated daily with a #19 Hegar's dilator for 3 months.

Results

Each of the 67 children with colitis experienced marked clinical improvement after resection of the diseased colon

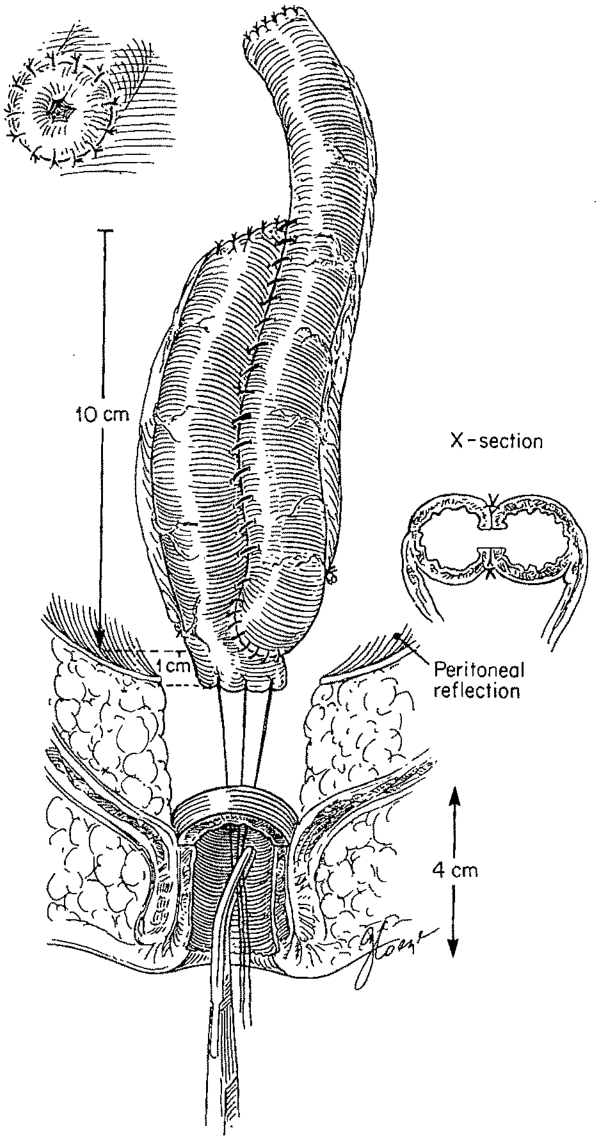

FIG. 2. The entire reservoir anastomosis is oversewn with a second layer of continuous or interrupted Maxon. Traction sutures on the ileal spout are drawn through the rectal muscle to the anus. The full thickness of the ileal spout is sutured to the anal mucosa and muscularis with interrupted 2–0 Vicryl (Ethicon). A completely diverting ileostomy is placed approximately 10 cm above the reservoir.

and rectal mucosa. There have been no deaths in the perioperative period or in long-term follow-up. The most common complication after the pullthrough procedure was ileoanal stenosis causing reservoir outlet obstruction, which occurred in 14 children (17%). Eight of these patients were successfully treated by daily rectal dilatation; six required at least one dilatation under general anesthesia. An elongated ileal spout of more than 2 cm length was believed to be the major cause of outflow obstruction in two children. A large ileal reservoir constructed at the initial operation (>15 cm) was implicated as the major cause of incomplete reservoir emptying and stasis in four. A combination of outflow obstruction and reservoir enlargement were believed to have contributed to stasis with chronic reservoir inflammation in 14 children. Intestinal adhesions, internal hernias, or intussusception occurred in 10 children. Wound infections were present in seven children. Ileostomy obstruction after the first operation occurred in four children. Three children developed peripullthrough sinus tracts originating at the ileoanal anastomosis. Forty-three children (52%) experienced complications, with 11 having more than one.

Twenty-seven of the seventy-six children with a lateral reservoir and five of the six patients with a straight pullthrough procedure required subsequent reoperation (39%). Twenty-two children required a subsequent operation within 2 years after closure of the ileostomy (27%), and 10 additional children required reoperation more than 2 years after the original procedure (12%). Eleven children underwent two or more reoperations. It is noteworthy that 60% of the complications requiring operation occurred in the first 30 patients. Only 8% of the last 40 children have required reoperation.

Almost all children with an initial reservoir length of more than 15 cm developed progressive pouch enlargement with fecal stasis, diarrhea, bacterial overgrowth, increased gas production, and symptoms of frequency, urgency, nausea, and occasional incontinence. Most of these patients progressed well for the first 12 to 18 months, with five to eight bowel movements per day until the reservoirs became so large that they emptied only small amounts with each defecation. In six children, elongated reservoirs were shortened during the ensuing 5 years to a length of 12 cm or less by resecting the upper end of the reservoir and anastomosing the end of the ileum to the remaining reservoir. Two children had transanal shortening of the ileal reservoir spout alone. Ten patients had both shortening of the elongated reservoir as well as the spout to alleviate reservoir outlet obstruction.

Five of the six children with straight pullthrough procedures experienced persistent stool frequency and urgency, often accompanied by soiling, and required reoperation with conversion to an LR. Four of these children had UC and one had polyposis.

Four of the eighty-two children were returned to a permanent ileostomy (4.9%) with removal of the reservoir; two of these patients were eventually proven to have Crohn's disease instead of UC. Ten of the eighty-two children were returned to a temporary ileostomy because of various complications or to encourage catch-up growth during the adolescent years; seven of the ileostomies have subsequently been closed without sequelae. Thus, 74 of the 82 children currently have a functioning LR and one a straight pullthrough procedure.

Each of the 75 children with a functioning ERP (91.5%) are currently progressing well. Most have between three and five continent movements per 24 hours (mean, 4.8 per 24 hours). Less than 15% experienced daytime soiling by 3 months, although 35% had occasional soiling episodes in the nocturnal hours. By 6 months, less than 14% experienced nocturnal soiling. By 24 months, seepage or incontinence were very rare. Thirty-four of the patients participate in active or vigorous athletic activities. None of the boys has experienced impotence or evidence of retrograde ejaculation. Three of the girls have delivered healthy full-term babies within 3 years after operation, two by vaginal approach. Measurements of fecal bile salts and serum B_{12} levels have been within normal range in the 19 children in whom these studies were evaluated. Detailed review of the last 45 consecutive children shows that all but two are currently functioning well, indicating the decreased number of complications as our clinical experience has increased.

Discussion

Although many of the manifestations of chronic UC can be improved appreciably by medical therapy, including corticosteroids, immunosuppressive drugs, parenteral nutrition, and other therapy, the vast majority of children will not be cured unless the colon and rectum are removed. There has been great reluctance by parents, pediatricians, and gastroenterologists to consider a procedure so extensive as proctocolectomy unless absolutely necessary to save the child's life.

During the past few years, however, it has become increasingly evident that a child's growth and development may be markedly delayed by the debilitating effects of colitis, and additionally there may be serious consequences of chronic administration of steroid and immunosuppressive medications. If operation to cure the disease is not performed before mid to late adolescence, the child may never have an opportunity to experience "catch-up" growth and may bear the consequences of childhood medical therapy for life. As a result of the delay in growth and maturation, the child may develop feelings of inferiority and a lack of desire to participate in many social and physical activities.

Because most children with severe UC continue to have symptoms into adulthood and eventually require proctocolectomy, serious consideration should be given to removing the colon and curing the disease during childhood before the epiphyses have closed. Children with severe chronic UC are rarely cured without operation. Catch-up growth and rehabilitation socially and physically often have been dramatic after removing the diseased colon and rectum during childhood, as noted in our series of patients.

A major concern of children with severe colitis who have been recommended for colectomy is that they will be required to wear an ileostomy appliance for life. Although the care of an ileostomy is usually easily mastered by a child, the presence of the stoma appliance often serves as a source of embarrassment during physical and social activities. Furthermore, there is great concern among adolescent boys that proctocolectomy carries a risk of impotence. Although postoperative impotence or bladder dysfunction after proctocolectomy in childhood are uncommon, these concerns have influenced many children to defer operation until they are severely debilitated by the colitis or steroid therapy, and may manifest irreversible systemic complications. Because four children who had undergone previous proctocolectomy with permanent ileostomy in other hospitals requested evaluation for the ERP, it would appear prudent to discuss all surgical options before performing proctectomy on any child with polyposis or UC. As noted in the present series, no patient developed bladder dysfunction, impotence, or retrograde ejaculation; however, three children were so obese or had other complications related to medical therapy that the ERP could not be safely undertaken.

As noted by Orkin and associates,[5] the complications after surgical management of UC in children increases with the duration of the disease and the length and dosage of medications. It is very evident from the present series of patients that those receiving long-term corticosteroids and immunosuppressive drugs have a considerably higher complication rate than do those children who have received shorter courses of therapy. This is further supported by the fact that only two of the 14 children with polyposis who underwent the ERP developed complications requiring reoperation (14%), whereas 30 of 67 patients with UC (45%) required reoperation.

Subtotal colectomy with ileorectal anastomosis is no longer recommended as an option for children with UC because almost all will experience continued severe disease in the rectum requiring medical therapy and eventual surgical removal. Although the ileorectal anastomosis has been used extensively for children with colonic polyposis, there is increasing evidence that the ERP with reservoir provides lower stool frequency and urgency. Furthermore, patients with polyposis will require frequent endoscopic examination of the remaining rectal segment for life because the rectum is at high risk for eventually developing carcinoma.

There was initial enthusiasm for the Kock continent ileal reservoir following proctocolectomy for children with UC; however, complications related to stasis and distention from incomplete emptying, pouchitis, and incompetence of the nipple valve have led to multiple reoperations and eventual removal in many patients. The procedure is currently reserved for those children who already have a permanent ileostomy and who are greatly handicapped by its presence.

Although some surgeons report that the straight ERP produces continence with similar stool frequency as when a reservoir is used, our clinical experience has been quite different.[7,9] Five of the six children with a straight pullthrough had such severe frequency, urgency, and eventually incontinence that they requested the pullthrough be discontinued and that an ileostomy be constructed. Each of these five children underwent successful surgical conversion to an LR. Occasional children will have an acceptable result without a reservoir; however, it is difficult to identify these patients preoperatively and accordingly we recommend use of a reservoir in all children.

Although a variety of ileal reservoirs are currently in clinical use (S-shaped, J reservoir, W pouch, and lateral reservoir), with somewhat comparable early results with respect to stool frequency and continence, it has become apparent that pouchitis is more common in larger reservoirs that empty only partially with each defecatory movement.[10] In contrast to colonic mucosa, ileal reservoir mucosa becomes inflamed when stasis and bacterial overgrowth occur, leading to diarrhea, urgency, frequency, and occasional incontinence. Although many children will be relieved of symptoms by adherence to a constipating diet and use of antidiarrheal medications, metronidazole, bulking agents, and rectal irrigations, the symptoms usually recur when only partial emptying occurs. Stenosis of the ileoanal anastomosis or lower end of the reservoir may appear to be mild, annoying problems but can cause reservoir distention, stasis, and pouchitis, if not corrected early. Our patients therefore have used a rectal dilator on a daily basis for the first 3 months after operation.

Gradual enlargement of the ileal reservoir during the first year is anticipated regardless of the configuration. Because the daily fecal output for most children with an ERP varies between 600 and 800 mL, reservoirs with a capacity of more than 300 mL would appear to be unnecessary and may be counterproductive. Reservoir enlargement of sufficient magnitude to produce chronic pouchitis may not become evident for more than a year after operation, however, when symptoms persist despite therapy, operative shortening of the reservoir and ileal spout may relieve the pouchitis permanently, as with 19 children in this report.

The LR lends itself particularly well to the shortening procedure; no major complications occurred in any of the patients. Our limited experience with reservoir modification or shortening for the SR and JR in older patients have been less successful because of the more complex vascular supply to the lower end of the reservoir.[11] Further advantages of the LR over the J reservoir in our experience are that it is easier to bring the end of the ileum to the anus with minimal tension, an end anastomosis of the ileum to the anus is easier technically than is a lateral anastomosis, it is technically easier to construct a short ileal pouch, and the pouch is tapered in the rectal muscle canal.

Almost all complications after the ERP are surgically correctable when recognized and treated early. Most major complications occurred in the first 30 patients and were attributed to the large size of the reservoir and long ileal spouts. The two children with UC who were returned to a permanent ileostomy were from our first 10 patients, and most likely could have undergone successful reconstruction. This low incidence of pouch failure compares favorably with the 6% to 13% failure rate reported in large series of adult patients.[12,13] Temporary ileostomy may be necessary in certain children, particularly if growth and development during adolescent years is not progressing at an optimal rate. After the reservoir reconstruction has been completed and the child has returned to a steady progress upward on the growth curve, the ileostomy can be safely closed in almost all cases.

Fewer complications have occurred during the past 5 years with the use of a short rectal muscle cuff, a short ileal reservoir (10 cm), a short ileal spout (<1 cm), and removal of all rectal mucosa down to the dentate line. On the basis of our experience with the ERP in 82 children, the long-term postoperative results are slightly better than in adult patients. Follow-up for many years is necessary to recognize some of the more insidious complications of the ERP procedure, although it appears to be an excellent alternative to proctocolectomy with permanent ileostomy for the treatment of UC and polyposis coli in childhood.

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Morbidity and Mortality After Pelvic Exenteration for Colorectal Adenocarcinoma

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A retrospective analysis was made of the complications from pelvic exenterations performed over the past 30 years for colorectal adenocarcinoma at the Roswell Park Cancer Institute. Seventy-five patients underwent exenteration, 51 for primary disease (PD) and 24 for recurrent disease (RD). Both total and posterior exenterations were included. Twenty of the fifty-one patients (39%) undergoing exenteration for PD developed severe complications, with an operative mortality rate of 6%. The most common complications were injuries to the ureter or bladder, intra-abdominal abscesses, and anastomotic leaks from the urinary diversion. After exenteration for RD, 12 of 24 patients (50%) developed severe complications, with an operative mortality rate of 4%. The most common major complication was an anastomotic leak from the urinary diversion; this occurred in 33% of all patients with RD (8/24). The authors conclude that, although exenteration for colorectal adenocarcinoma may be performed with a low operative mortality rate, patients must be carefully selected because the associated morbidity rate remains high.

PELVIC EXENTERATION FOR colorectal adenocarcinoma confined to the pelvis remains a formidable procedure today, 40 years after its initial description.[1,2] Patients with bulky and locally advanced pelvic disease are often symptomatic. Aggressive surgical extirpation, whether performed for primary treatment or for recurrent disease, often represents the best treatment option for patients. An adequate understanding of the potential complications associated with these procedures, however, is mandatory. We have analyzed a 30-year experience with pelvic exenteration at the Roswell Park Cancer Institute in an effort to provide such information.

Materials and Methods

This is a retrospective review of the medical records of patients who underwent pelvic exenteration for primary or recurrent colorectal adenocarcinoma from January 1960 to March 1990 at the Roswell Park Cancer Institute. This included both total exenteration and posterior exenteration. Total pelvic exenteration was defined as the extirpation of the rectum and bladder in men, as well as the uterus (if present) in women. Posterior pelvic exenteration was defined as the extirpation of the rectum, uterus, and ovaries in women. The indications for total pelvic exenteration were either documented involvement of the base of the bladder or trigone, based on the preoperative workup, or suspected involvement on intraoperative evaluation. Only those patients who required a total cystectomy were included in the analysis of this group. The indications for posterior exenteration for primary disease included anterior or circumferential lesions in women. Suspected vaginal or uterine involvement based on intraoperative evaluation was an indication for posterior exenteration in both primary and recurrent disease.

Before exenteration, all patients underwent a mechanical bowel preparation with preoperative prophylactic antibiotics. After total exenteration, the urinary diversion was performed with a small bowel loop conduit and separate end-to-side ureterointestinal anastomoses with fine interrupted absorbable sutures as described by Bricker and Modlin.[1] Ureteral stenting usually was not performed, but there was drainage of the retroperitoneal space with Penrose and active sump drains. If a perineal dissection was required, the perineal wound was packed open and healed by secondary intent.

Surgical morbidity and mortality rates were defined as occurring within 30 days of the pelvic exenteration. Major morbidity was defined as a significant complication whose treatment required surgery, prolonged the hospital stay,

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or led to an alteration in that patient's management. All other complications were categorized as minor morbidity.

Results

Seventy-five patients underwent pelvic exenteration. There were 17 men and 58 women. The mean age was 60 years, with a range of 19 to 83 years. Fifty-one patients underwent exenteration for primary disease and 24 for recurrent disease. Of the 51 patients with primary disease, 14 underwent total pelvic exenteration, whereas 37 patients received a posterior exenteration. Of the 24 patients with recurrent disease, 14 underwent total pelvic exenteration and 10 patients received a posterior exenteration. The TNM (tumor, nodes, and metastases) classifications[3] of both groups are listed in Table 1. The classification for patients with recurrent disease refers to the original primary tumor.

The overall major morbidity rate in this series was 32 of 75 patients (43%). After exenteration for primary disease, 20 of the 51 patients (39%) developed severe complications, with three surgical mortalities (6%). The types of complications are listed in Table 2. The most common major complications were iatrogenic injury to the bladder or ureter, intra-abdominal abscesses, and abdominal wound infections. There were three anastomotic leaks, two from the ureteroenterostomy and one from the enteroenterostomy anastomosis after formation of the urinary conduit. One patient underwent a total pelvic exenteration with aortic and iliac lymph node dissection; he developed intra-abdominal hemorrhage from necrosis of the right common iliac artery, which was successfully repaired. More than one complication occurred in some patients, as noted by the total number of complications. Twelve of these twenty patients developed complications that required surgery (60%). These are noted in Table 2. The minor complications incurred after exenteration for primary disease are listed in Table 3. Urinary tract infections and neurogenic bladder were the most common minor complications. When included with major morbidity, 36 of 51 patients (71%) undergoing exenteration for primary disease developed a complication.

After exenteration for recurrent colorectal adenocarcinoma, 12 of 24 patients (50%) developed severe com-

TABLE 1. *Stage of Primary Tumor*

TNM	No. of Patients Exenteration for Primary Disease	Exenteration for Recurrent Disease (Stage of Primary Tumor)
(TIS)	0	0
(T1/T2, NO)	11	3
(T3, NO)	6	9
(T4, NO)	15	1
(T1-3, N1)	6	3
(T1-3, N2)	2	3
(T4-, N1-2)	9	3
(any T, any N, M1)	2	1
Unknown	0	1

TABLE 2. *Major Morbidity After Pelvic Exenteration*

Complication	Primary Disease No. of Patients* No Surgery (Surgery)	Recurrent Disease No. of Patients* No Surgery (Surgery)
Ureteroenterostomy or enteroenterostomy anastomotic leak	3 (2)	8 (7)
Iatrogenic injury to bladder (3 patients+) or ureter (2 patients+)	5+ (3)	1
Intra-abdominal abscess	4 (2)	1
Necrotizing fasciitis	2 (2)	—
Small bowel obstruction secondary to adhesions	2 (2)	2 (2)
Wound dehiscence	2 (2)	2 (1)
Massive lower gastrointestinal hemorrhage, cause unknown (subtotal colectomy performed)	1 (1)	—
Small bowel fistula secondary to bowel obstruction	1 (1)	—
Wound infection	4	2
Pneumonia	1	1
Vascular insufficiency requiring extremity amputation	—	1 (1)
Intra-abdominal hemorrhage secondary to external iliac artery stump disruption	—	1 (1)
Ruptured right common iliac artery	1 (1)	—
Revision of ileostomy	1 (1)	—
Total	27	19

* More than one complication occurred in some patients.

TABLE 3. *Minor Morbidity After Pelvic Exenteration**

Complication	Primary Disease No. of Patients†	Recurrent Disease No. of Patients†
Small bowel obstruction	1	—
Neurogenic bladder	5	3
Urinary tract infection	8	2
Central venous catheter sepsis	1	—
Common peroneal nerve neuropraxia	1	2
Gastrointestinal hemorrhage	1	—
Vaginal-perineal fistual	—	1
Staphylococcus enteritis	1	—
Supraventricular tachycardia	1	—
Contact dermatitis secondary to betadine	1	—
Total	20	8

* No surgery required for resolution.

† More than one complication occurred in several patients.

plications, with one surgical death (4%). The types of complications are listed in Table 2. The most common major complication was ureteroenterostomy or enteroenterostomy anastomotic leak after urinary conduit formation, which required surgery in 7 of 8 patients. Two patients had both a ureteroenterostomy and enteroenterostomy leak. Two additional patients had enteroenterostomy leaks, and four patients had ureteroenterostomy leaks. Again, more than one complication occurred in some patients. Eight of the twelve patients (67%) who developed complications required surgery. The minor complications that developed in this group are listed in Table 3. The most common minor complication after exenteration for recurrent disease was neurogenic bladder. When included with major morbidity rate, 20 of 24 patients (83%) undergoing exenteration for recurrent disease developed a complication.

Eleven of the seventy-five patients (15%) had received prior radiation to the abdomen or pelvis–perineum. This included three of 51 patients (6%) in the group with exenteration for primary disease and eight of 24 patients (33%) undergoing exenteration for recurrent disease. The indications and possible complications that resulted from radiation in each group are shown in Table 4. Of the three patients with prior irradiation who underwent exenteration for primary disease, one (33%) developed a complication of ileostomy stomal retraction. Of the eight patients with prior irradiation who underwent exenteration for recurrent disease, all (100%) developed a complication. Of the 16 patients with no prior irradiation undergoing exenteration for recurrent disease, 10 (63%) developed a major complication.

Among the three surgical deaths in the primary disease group, all were sepsis related (abdominal abscess, necrotizing fasciitis, and pneumonia, respectively). The single death of recurrent disease died of intra-abdominal hemorrhage secondary to rupture of a previously ligated external iliac artery after an *en bloc* resection and femoral to femoral artery bypass.

Discussion

Pelvic exenteration for locally advanced pelvic cancer was first described by Brunschwig in 1948.[2] Only one of the 22 patients in this series had a tumor of colorectal origin; the remainder were gynecologic carcinomas. The operative mortality rate was 23%. Appleby[4] applied the same surgical principles when he reported a series in 1950 of eight male patients who had undergone "proctocystectomy." Although the morbidity rate was not reported, the operative mortality rate was 17%. In all of these patients, the urinary stream was diverted into the sigmoid colon, producing a "wet colostomy." The procedure has evolved in the 42 years since it was first described. Chief among the innovations was the development of the ileal loop conduit for urinary diversion by Bricker in 1951.[1]

Pelvic exenteration for colorectal adenocarcinoma remains a formidable procedure. The indications at the Roswell Park Cancer Institute include locally advanced disease, with clinical or presumptive involvement of adjacent organs. This procedure may be performed for either primary or recurrent disease. In either case, tumor should be limited to the pelvis. Presently, contraindications at our Institution include tumor involvement of the pelvic sidewall, pubic symphysis, or major vessels or nerves. Sciatic or perineal pain suggestive of nerve root involvement are not considered amenable to this procedure. The natural history of recurrent disease that involves the sacrum, although technically resectable in some cases, is not altered by pelvic exenteration.[5] Unilateral or bilateral hydronephrosis in recurrent disease may be a relative contraindication.[6] The size of the tumor mass, involvement of

TABLE 4. *Possible Radiation Complications*

Patient	Total Radiation Dose (rad)	Indication	Complication
Primary disease			
1	4320	Adjuvant rectum	None
2	3000	Prior uterine cancer	None
3	Unknown	Prior cervical cancer	Ileostomy retraction requiring surgical revision
Recurrent disease			
1	2500	Only treatment to rectal primary lesion	Neurogenic bladder*
2	5000	Adjuvant rectum	Neurogenic bladder*
3	2100	Adjuvant rectum (to liver only)	Anastomotic leak
4	5000	Pelvic recurrence	Wound dehiscence
5	8000	Pelvic recurrence	Anastomotic leak
6	Unknown	Pelvic recurrence	Neurogenic bladder*
7	Unknown	Pelvic recurrence	Anastomotic leak wound dehiscence
8	4000	History of Hodgkin's disease	Anastomotic leak, small bowel obstruction

* More likely secondary to surgical dissection rather than to radiation.

adjacent organs, previous surgery, and prior irradiation are all factors that may lead to substantial morbidity and mortality rates.

In this retrospective analysis of 75 patients undergoing pelvic exenteration for colorectal adenocarcinoma over a 30-year period, the overall operative mortality was 5%; that for primary disease, 6%; and for recurrent disease, 4%. A previous report from our Institution noted a 10% operative mortality rate among 30 patients undergoing pelvic exenteration for primary colorectal malignancies.[7] Reports in the literature may be confusing when results from colorectal adenocarcinomas are combined with primary anal canal and gynecologic tumors, and when results from total, posterior, and anterior exenterations are not distinguished. Moreover, we believe that exenteration for primary disease should be considered separately from exenteration for recurrent carcinoma. Both mortality and morbidity rates can be expected to be higher in the latter patients. Recurrent tumors can attain considerable size and further complicate the technical aspects of a repeat procedure. In addition, many of these patients will have undergone prior radiation therapy, adding to the hazard of this procedure.

Lopez et al.[8] reported an operative mortality rate of 21% for total pelvic exenteration in primary rectosigmoid carcinoma over a 30-year period; this decreased to 9% in the final decade. Boey et al.[9] found a 15% 30-day mortality rate in a similar group of patients. Mortality rates range from 0% to 18% in series that also include tumors not of colorectal origin (Table 5)..[4,6–17] All three of the surgical deaths in our present series for primary disease were related to sepsis: abdominal abscess, necrotizing fasciitis, and pneumonia. None of these patients had a clinically recognized anastomotic leak to explain their subsequent course. The single operative death among patients with recurrent disease succumbed after an iliac artery graft anastomosis dehisced. This had originally been placed after an *en bloc* resection of a portion of the artery with the tumor.

Although the operative mortality rate was low in our experience, a considerable number of our patients developed complications. After exenteration for primary disease, 39% developed major complications, of which 60% required surgery. Among patients with recurrent disease, 50% developed complications that met our criteria for major morbidity, of which 67% required surgery. When minor complications are included, the overall morbidity rate for primary and recurrent disease was 71% and 83%, respectively. Because the criteria for postoperative morbidity may vary among authors, we have attempted to categorize our complications into major and minor groups in an admittedly subjective fashion. Major morbidities were those that required surgery, prolonged hospitalization, or were thought to have caused a significant change in patient management. We believe that when interpreting morbidity data for the individual patient, such "major" factors are most likely to affect the physician's decision to select a particular operation.

With these caveats in mind, the reported morbidity rates vary widely in the literature, ranging from 13% to 77%.[1,7,12–14,18] Complications related to the urinary diversion were most often cited.[7,9,14,15] Gastrointestinal complications, particularly small bowel obstruction and fistulas, are also commonly reported.[8,9,13–15]

A ureteroenterostomy or enteroenterostomy anastomotic leak occurred in eight of 24 patients (33%) with recurrent tumor in our series. An additional element in those patients with recurrent disease who developed anastomotic leaks was a history of prior radiation therapy. Four of the eight patients (50%) who developed an anastomotic leak received radiation therapy. Radiation therapy had been used in only 15% of our patients before their exenteration, although fully one third of those with recurrent disease had been so treated. It may have been

TABLE 5. *Reported Data on Pelvic Exenteration for Colorectal Adenocarcinoma*

Reference	Year	Primary Lesion	Surgery/indication	No. of Patients	Morbidity (%)	Mortality (%)
Appleby[4]	1950	CR	TPE/PD	6	—	17
Brintnal and Flocks[10]	1950	CR	TPE/PD	9	—	33
Kiselow et al.[11]	1967	CR	TPE/PD	43	—	16
Olsson et al.[12]	1976	CR + bladder + cervix	TPE, AE/PD, RD	18 (7 CR)	45*	6
Eckhauser et al.[13]	1979	Rectum	TPE, PE/PD	12	75*	8
Ledesma et al.[7]	1981	CR, anus	TPE/PD	30	13	10
Boey et al.[9]	1982	CR	TPE, PE/PD	49	51	18
Jakowatz et al.[14]	1985	CR + others	TPE, PE, AE/PD, RD	104 (31 CR)	49	3
Lindsey et al.[15]	1985	CR + others	TPE, PE, AE/PD, RD	68 (29 CR)	30	14
Takagi et al. [16]	1983	CR	TPE/PD	13	—	8
Lopez et al.[8]	1987	CR	TPE/PD, RD	24	26	20
Hafner (current series)	1991	CR	TPE, PE/PD, RD	75	43	5

* Includes early and late complications.

CR, colorectal; TPE, total pelvic exenteration; PD, primary disease; AE, anterior exenteration; RD, recurrent disease; PE, posterior exenteration.

involved in one complication for primary disease, where a retracted ileostomy required surgical revision. However, technical errors during the initial surgery also could have contributed to this complication. Additionally, three patients with recurrent disease who received prior radiation developed a neurogenic bladder, but this complication was more likely secondary to nerve injury during the pelvic dissection.

Other groups have found radiation therapy to be a significant complicating factor. Jakowatz et al.[14] noted that 49% of their pelvic exenterations developed complications involving the gastrointestinal tract, urinary tract, or abdominal wound. Prior radiation led to a much higher morbidity rate compared with those without such treatment (67% *versus* 26%, respectively). This group recommended reconstruction of the irradiated pelvis by an omental flap, colonic advancement, or a myocutaneous flap to decrease the complication rate. Lopez et al.[8] reported that three of four patients (75%) with and two of 15 patients (13%) without prior irradiation who survived the operation had major complications ($p < 0.005$).

It has been shown in our series and others that pelvic exenteration may be carried out with a low mortality rate. We have reported a significant morbidity rate for both primary and recurrent disease. Radiation therapy was used in relatively few of these patients, but may have contributed to the morbidity rate. With the recent National Institutes of Health (NIH) consensus on adjuvant radiation and chemotherapy for stage II and III rectal adenocarcinoma,[3] the treatment of local-regional recurrence will be largely limited to surgery. We continue to advocate an aggressive posture for locally advanced colorectal adenocarcinoma, whether for primary or recurrent cancer. Our data do serve to emphasize, however, that careful patient selection is imperative before undertaking a procedure of this magnitude.

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Prognostic Factors Influencing Survival in Gastrointestinal Leiomyosarcomas

Implications for Surgical Management and Staging

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The appropriate surgical therapeutic options for either localized or more advanced disease in patients with gastrointestinal leiomyosarcomas remain unclear. A staging classification for this disease has not been adopted nor risk factors identifying patients at risk for recurrence defined. To address these issues, this study evaluated the influence of various clinicopathologic variables on overall and disease-free survival. In an univariate analysis of overall survival involving 191 patients, the Cox proportional hazards model identified four factors that were associated with a significantly better outcome: complete resection without tumor rupture ($p < 0.001$), localized lesions ($p < 0.001$), low grade of tumor ($p = 0.02$), and tumors smaller than 5 cm ($p = 0.03$). When interactive effects of these factors were taken into account, however, type of resection of the tumor was selected as the only significant prognostic factor in a multivariate analysis. Complete resection without tumor rupture improved overall survival of patients with localized disease (median, 46 months) as well as those with contiguous organ invasion (median, 36 months) or peritoneal implants (median, 36 months). In contrast, patients with incomplete resections survived for a median of 21 months. Patients with tumor rupture, despite removal of all gross disease, behaved similarly to those with incomplete resections; median survival was only 17 months. For disease-free survival, important determinants selected from a multivariate analysis were tumor rupture ($p = 0.002$), contiguous organ invasion ($p = 0.02$) and high tumor grade ($p = 0.02$). A staging classification incorporating these prognostic factors of significance was evaluated using a TGM system: T1 (<5 cm), T2 (≥5 cm), T3 (contiguous organ invasion or peritoneal implants), T4 (tumor rupture); G: G1 (low grade), G2 (high grade); M: M0 (no metastases), M1 (metastases present). The corresponding 5-year overall survivals for stages I, II, III, IVA, and IVB were 75%, 52%, 28%, 12%, and 7%. Disease-free survival at 2 years after surgery was 89%, 57%, and 47% for stages I, II, and III, respectively. In conclusion, surgery remains the primary modality of treatment for patients with gastrointestinal leiomyosarcomas, and complete resection of all disease without tumor rupture, even of locally advanced disease, improves overall and disease-free survival. A staging classification appears feasible and is recommended to determine outcome in patients with leiomyosarcomas arising from the gastrointestinal tract.

SURGERY REMAINS THE the primary modality of treatment for patients with gastrointestinal leiomyosarcomas. Therapeutic options for localized or more advanced stages of disease, however, have not been assessed with respect to clinical outcome. For example, the ability of radical extirpative surgery to improve survival of patients with primary tumor invading contiguous organ or associated with peritoneal implants remains in doubt. For localized lesions, unclear issues include the adequate extent of primary organ resection and the need for wide excision of attached mesentery or regional lymphadenectomy. Further, prognostic factors that can identify high-risk groups for recurrence, despite such "curative surgery," have not been elucidated. In contrast to soft tissue tumors arising from other sites,[1] a staging classification has not been adopted for gastrointestinal leiomyosarcomas. In an attempt to address these issues, this study evaluated the influence of various clinicopathologic factors, including type of surgery performed, on overall and disease-free survival. The results of these analyses are used in recommending rational therapeutic strategies for patients with gastrointestinal leiomyosarcomas. Finally, we also examined the feasibility of formulating a staging classification based on significant prognostic factors.

Methods

The records of all patients with gastrointestinal leiomyosarcomas referred to University of Texas M. D. An-

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derson Cancer Center (UTMDACC) from January 1957 to December 1987 were reviewed. All tumors with the diagnosis of leiomyosarcoma that originated from the gastrointestinal tract and were confirmed by a UTMDACC pathologist were included in this study. Primary tumors attached to the mesentery or omentum were also included and labeled as arising from an "other" site of origin. Patients with leiomyosarcomas arising from the retroperitoneum or esophagus or patients with other synchronous or metachronous malignancies were excluded. The last recorded date of follow-up was April 15, 1990. The median follow-up of surviving patients was 68 months (range, 15 to 178 months).

Definitions and Criteria

The tumor size used was as determined by the pathologist at the institution where the primary operation was performed. The tumor grade assigned and criteria for such grading was determined by the reviewing pathologist at UTMDACC at the time of patient referral. The type of operation performed was classified as complete resection with or without tumor rupture or incomplete resection. Complete resections were defined as removal of all gross disease at operation; conversely, incomplete resections implied gross residual disease remaining after surgery. Tumor rupture referred to those patients in whom complete resections were performed but the tumor ruptured either at the time of resection (n = 17) or because of perforation just before surgery (n = 7). Disease extent was determined intraoperatively. Localized lesions were confined to the primary organ of origin; contiguous organ involvement had to be confirmed by the histologic presence of primary tumor invasion. Resectable implants were peritoneal deposits within the abdominal cavity, excluding liver, and removable by surgery. Unresectable implants were lesions in similar location but not amenable to surgical removal. Metastases were either deposits in the liver noted at operation or in other extra-abdominal sites detected by appropriate investigations.

Statistical Methods

Survival curves incorporating various prognostic factors for overall and disease-free survival were computed using the methods of Berkson and Gage.[2] Zero time was at initial surgery; the terminal event was either death due to disease or initial recurrence, as appropriate. The Cox proportional hazards model was used in identifying factors of significance.[3] This was performed with effects of individual variables considered individually (univariate analysis) and when the joint effects of variables were modeled by Cox stepwise regression analysis (multivariate analysis). In the analysis of prognostic factors by site of tumor, comparison of survival experiences was performed using the Lee-Desu statistic.[4] P values < 0.05 were considered statistically significant.

Results

Patient Characteristics

During the study period, 201 patients with gastrointestinal leiomyosarcomas were referred to this institution for primary therapy, adjunctive therapy after surgery, or treatment of recurrences. Ten patients with either synchronous or metachronous secondary malignancies were excluded from this study. Secondary malignancies consisted of breast carcinoma (2), colorectal carcinoma (3), lymphoma (3), hepatocellular carcinoma (1), and urethral carcinoma (1). Demographic and clinical features of the patient population are listed in Table 1. After exclusions, 191 patients were included in this study and the median age was 54 years (range, 12 to 85 years). Caucasians were the predominant race (87%) and there was a mild male preponderance (1.4:1). Tumors arising from the stomach (38%) and small bowel (41%) were the most common sites of origin. Most patients were treated with adjuvant systemic chemotherapy (76%); some patients received regional therapy (hepatic arterial infusions or chemoembolization) or radiotherapy for recurrences. The response to these therapies were marginal, and results of chemotherapy administered in a adjuvant setting or for recurrences were not thought to alter the clinical outcome.[5]

Overall Survival

All Patients. **Univariate Analysis.** Actuarial 5-year survival for all patients was 28% (Fig. 1). The median survival

TABLE 1. *Characteristics of Patient Population* (n = 191)

Characteristic	N (%)
Sex	
M	110 (58)
F	81 (42)
Ethnicity	
White	167 (87)
Black	9 (5)
Hispanic	12 (6)
Other	3 (2)
Age	
12–39	32 (17)
40–49	37 (19)
50–59	54 (28)
60–69	42 (22)
≥70	26 (14)
Site of primary lesion	
Stomach	72 (38)
Small bowel	79 (41)
Large bowel	22 (12)
Other	18 (9)
Chemotherapy	
Yes	145 (76)
No	30 (16)
Unknown	16 (8)
Radiation therapy	
Yes	38 (20)
No	130 (68)
Unknown	23 (12)

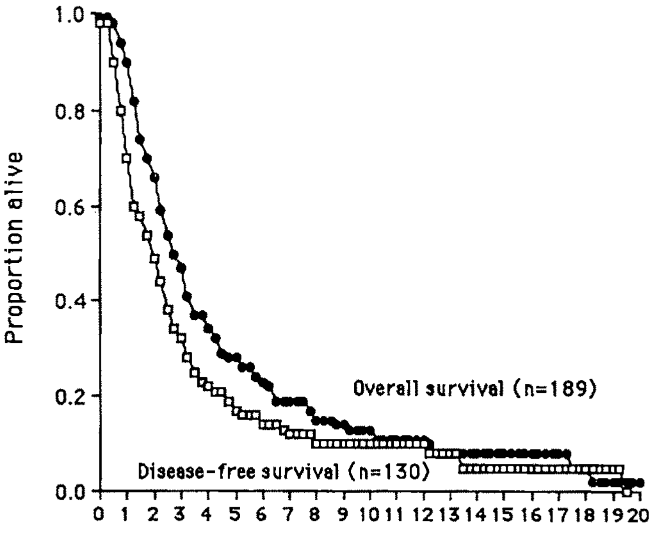

FIG. 1. Overall and disease-free survival rates for entire cohort. Disease-free survival based on patients with complete resection with and without tumor rupture.

time of the entire cohort was 29 months (range, 1 to 284 months). Seven prognostic factors were analyzed: type of operation, extent of disease, tumor grade, and tumor size correlated significantly with overall survivorship (Table 2).

Patients with complete resections showed improvements in overall survival (median, 48 months) compared with incomplete resections (median, 21 months; $p < 0.001$; Fig. 2). Tumor rupture at the time of surgery, despite the removal of all gross disease, was associated with an adverse influence on overall survival (median, 17 months). Progressive extent of disease at the time of surgery showed a stepwise inverse correlation with overall survival (Table 2 and Fig. 3). Localized tumors were associated with a favorable outcome and a median survival of 46 months. In contrast, patients with unresectable peritoneal implants or metastases experienced median survivals of 23 and 19 months, respectively. Tumor grade was also significant in predicting overall survival ($p = 0.018$, Fig. 4). The median survival of patients with low-grade tumors was 41 months, compared with 36 months for those with high-grade tumors. Patients with tumors smaller than 5 cm also experienced prolonged survivals (median, 68 months) when compared with patients with 5- to 10-cm tumors (median, 32 months) or greater than 10 cm (median, 27 months; Fig. 5). Site of origin, age, and sex were not significant prognostic factors (Table 2).

Multivariate Analysis. Only patients with complete information regarding type of operation, extent of disease, tumor grade, and size could be included in a stepwise regression analysis to evaluate the relative importance of various prognostic factors. Because the grade of tumor was not specified in many patients, the sample size would have been significantly reduced if grade was included as a variable to be evaluated. To overcome this limitation, analysis was performed with and without grade of tumor entered into Cox's model. The corresponding sample size was 100 and 149 patients, respectively. From both sets of analyses, type of operation was selected as the only significant prognostic factor. Other factors entered subsequently into the model (extent of disease, tumor grade, and tumor size) did not provide additional information regarding survival. Patients with incomplete resections or tumor rupture had a relative risk for death of 3.4 (95% confidence interval, 2.0 to 5.79) when compared with patients with complete resections without tumor rupture (relative risk = 1).

Patients With Complete Resections Without Tumor Rupture. The influence of extent of disease, tumor grade, and size were evaluated in the subset of patients who had complete resection of tumor without rupture (n = 99 patients evaluable). Within this population, only grade of tumor was significantly associated with overall survival ($p = 0.03$). Extent of disease ($p = 0.07$) and tumor size ($p = 0.1$) did not significantly influence survival. Thus, survivorship of patients with contiguous organ invasion (median, 36 months) or peritoneal implants (median, 36 months) were not significantly different when compared

TABLE 2. *Univariate Analysis of Factors That Influence Overall Survival*

Prognostic Factor	Evaluable Patients N (%)	Median Survival (mo)	p
Type of operation			<0.001*
Complete resection with no tumor rupture	99 (59)	48	
Incomplete resection	46 (28)	21	
Complete resection with tumor rupture	22 (13)	17	
Extent of disease			<0.001*
Localized	92 (53)	46	
Contiguous organ	21 (12)	36	
Implants resectable	19 (11)	28	
Implants unresectable	6 (3)	23	
Metastases	36 (21)	19	
Tumor grade			0.018*
Low	40 (39)	41	
High	62 (61)	36	
Tumor size (cm)			0.034*
<5	11 (8)	68	
5–10	45 (32)	32	
>10	86 (60)	27	
Site of primary lesion			NS
Age (yr)			NS
Sex			NS

* Factors entered into Cox proportional hazards model for regression analysis of joint effects and selection of significant prognostic factors.

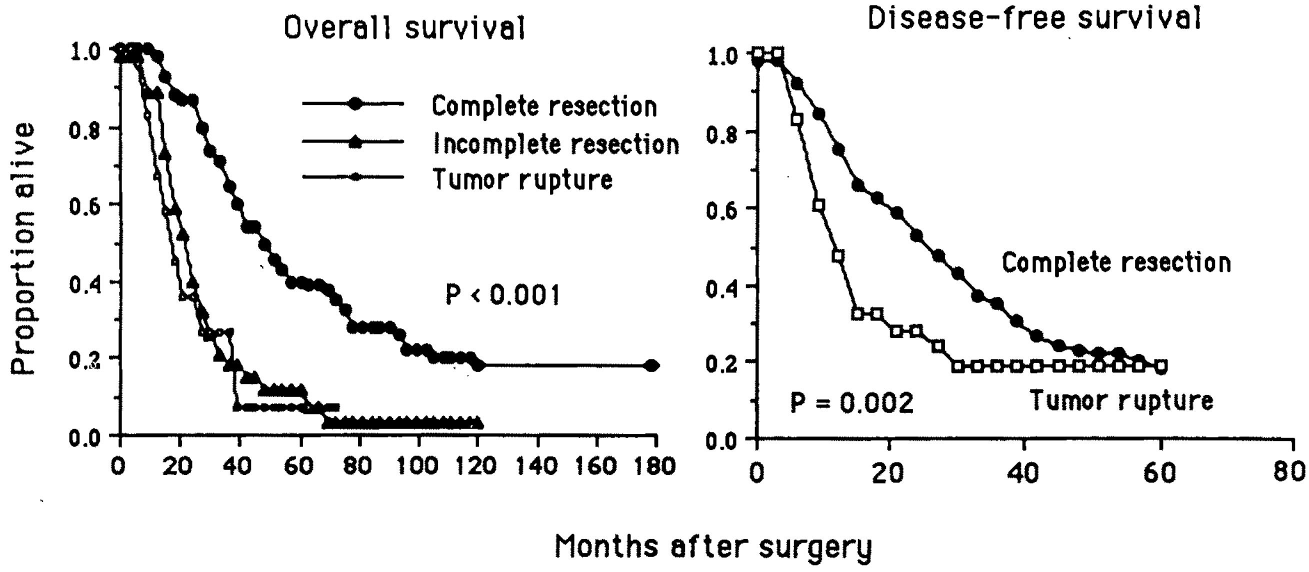

FIG. 2. Influence of type of operation on overall and disease-free survival rates. Complete resection without tumor rupture (n = 99); complete resection with tumor rupture (n = 22); incomplete resection (n = 46).

with patients with localized lesion (median, 46 months), provided that all primary tumor was removed without rupture.

Disease-free Survival

Univariate and Multivariate Analysis. Complete resections with and without tumor rupture were performed in 132 patients (69%) who were analyzed for factors influencing disease-free survival (Table 3). As of the last follow-up, only 10% of patients remained free of disease. The median interval to initial recurrence was 18 months (range, 3 to 232 months), and 60% of all recurrences occurred within 2 years of surgery (Fig. 1). Of the factors evaluated in a univariate analysis—tumor rupture (p = 0.002), extent of disease (p = 0.02), and tumor grade (p = 0.02)—were significantly related to disease-free survival. These three factors were each selected as significant factors in the multivariate analysis (Table 3). Tumor rupture had a dramatically adverse effect on disease-free sur-

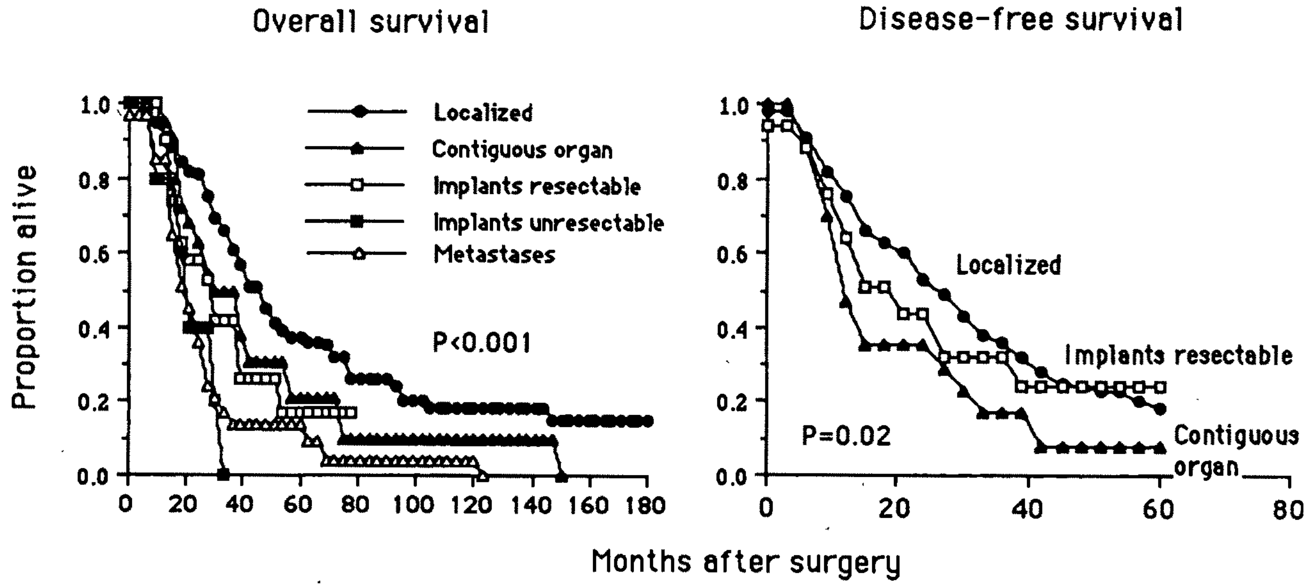

FIG. 3. Influence of extent of disease on overall and disease-free survival rates. Sample sizes for each category are shown in Table 2 for overall survival and Table 3 for disease-free survival.

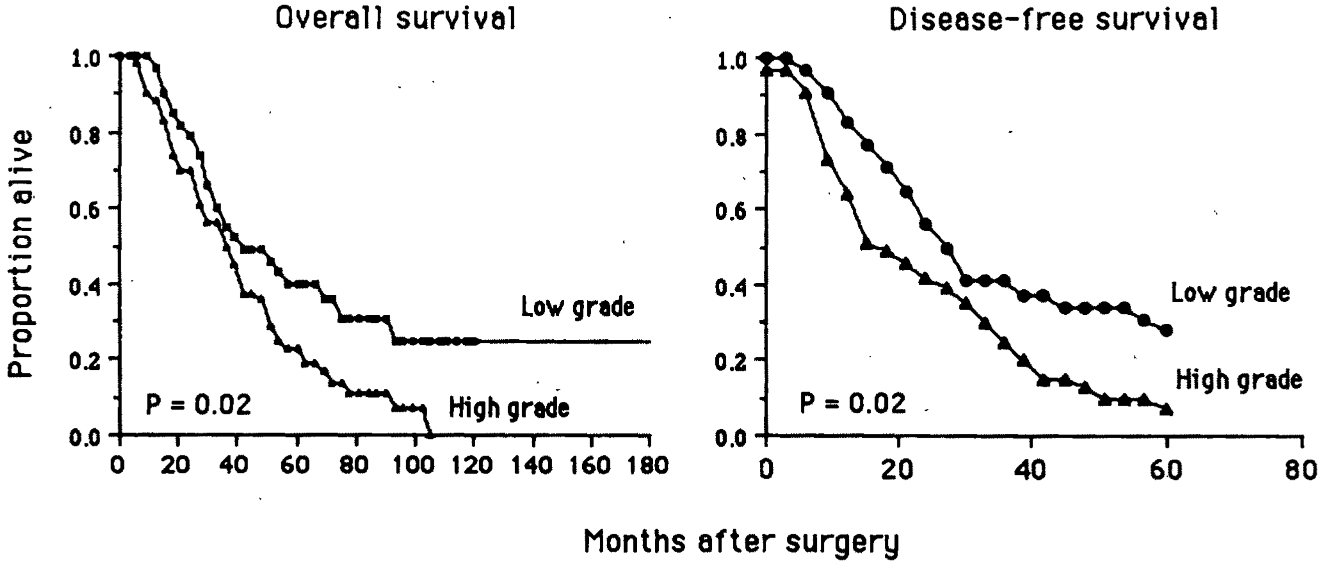

FIG. 4. Influence of tumor grade on overall and disease-free survival rates. Overall survival: low-grade (n = 40); high-grade (n = 61). Disease-free survival: low-grade (n = 36); high-grade (n = 45).

vival (median, 12 months) in comparison to patients without rupture (median, 26 months; Fig. 2). Patients with tumors that either invaded contiguous organs (median, 12 months; Fig. 3) or were high grade (median, 17 months; Fig. 4) experienced shorter disease-free survivals compared with localized (median, 27 months) or low-grade tumors (median, 27 months).

Analysis by Site of Tumor

An analysis of prognostic factors influencing overall survival was performed separately, based on the site of origin of the primary tumor: stomach (n = 72), small bowel (n = 79), and large bowel (n = 22; Table 4). Type of operation and the extent of disease were significantly related to overall survival in all primary sites analyzed. Tumor size was also significantly correlated with survival in stomach (p = 0.05) and large bowel (p = 0.04) tumors but not for small bowel tumors. Tumor grade showed significant trends only for tumors arising from the stomach (p = 0.07), but not for tumors arising from the small and large bowel.

The influence of the type of primary organ resection on overall survival and disease-free survival was evaluated

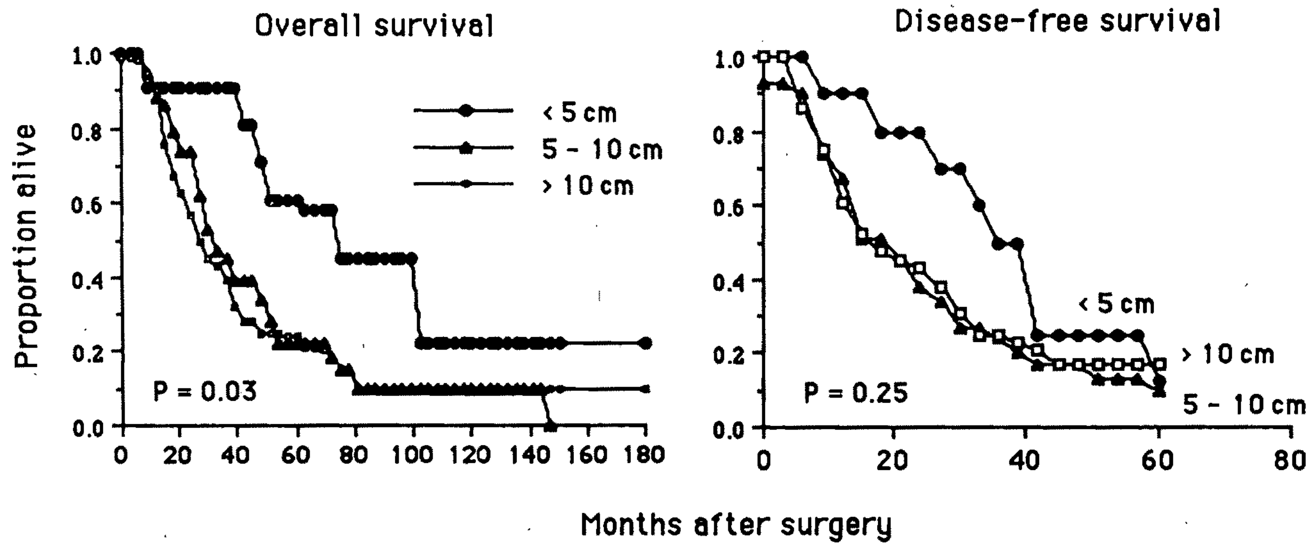

FIG. 5. Influence of tumor size on overall and disease-free survival rates. Sample sizes are shown in Table 2 for overall survival and Table 3 for disease-free survival.

TABLE 3. *Factors That Influence Disease-Free Survival After Complete Resection*

	Univariate analysis			Multivariate analysis*	
Prognostic Factor	Evaluable Patients N (%)	Median (mo)	p	Selected	Relative hazard†
Tumor rupture			0.002*	Yes	
No	99 (82)	26			
Yes	22 (28)	12			3.1
Extent of disease			0.02*‡	Yes	
Localized					
Implants	87 (73)	27			
resectable	17 (14)	19			
Contiguous organ	15 (13)	12			3.3
Tumor grade			0.02*	Yes	
Low	36 (44)	27			
High	45 (56)	17			1.9
Tumor size (cm)			NS		
<5	11 (10)	36			
5–10	31 (29)	19			
>10	66 (61)	17			
Site of primary lesion			NS		
Large bowel	16 (12)	39			
Stomach	45 (35)	25			
Small bowel	56 (43)	18			
Other	13 (10)	26			

* Prognostic factors entered into Cox model for regression analysis of joint effects and selection of significant prognostic factors ($p < 0.05$). Analysis was based on 72 patients with complete data.

† Relative risk of recurrence with reference to a value of 1 (no rupture, localized, and low-grade tumor).

‡ Localized *vs.* contiguous.

for tumors arising from the stomach and small bowel. The number of patients with large bowel tumors was too small for meaningful analysis. For appropriate comparisons, only localized tumors that were completely excised without tumor rupture were included. No differences were observed for wedge resections compared with more extensive surgery of the primary organ (gastrectomy or small bowel resection, Table 4). For stomach tumors, the median overall survival (67 months) and disease-free survival (33 months) after wedge resections were not statistically different after gastrectomy (median overall survival, 47 months; disease-free survival, 28 months; Fig. 6; $p = 0.26$). Similar results were observed when comparing for wedge resections against bowel resections for small bowel tumors (median overall survival, 75 *versus* 49 months; disease-free survival, 23 *versus* 26 months)

The impact of more radical locoregional surgery on outcome was also determined in the context of localized tumors. For tumors arising from the stomach, overall survival (median, 55 *versus* 41 months, $p = 0.65$, not significant [NS]) and disease-free survival (median, 33 *versus* 29 months, $p = 0.71$) were similar with or without resection of organs adjacent to the primary (Table 4 and Fig. 7). Similarly, no statistically significant differences were observed for small bowel tumors. Median overall survival and disease-free survival after resection of adjacent organs was 50 and 24 months, compared with 45 months ($p = 0.56$) and 26 months ($p = 0.7$) with surgery limited to the organ of origin, respectively.

Proposed Staging Classification

The ability of a staging classification incorporating prognostic factors of significance to stratify groups for overall and disease-free survival was examined. A TGM system was used for staging: T: T1, localized and <5 cm; T2, localized and ≥ 5 cm; T3, contiguous organ invasion or peritoneal implants; T4, tumor rupture. G: G1, low grade; G2, high grade. M: M0, no metastases; M1, metastases present. One hundred thirty-nine patients with complete data were evaluable for overall disease-free survival, and 93 patients were evaluable for disease-free survival. Plots of overall and disease-free survival curves for various combinations of the TGM system were generated: five composite stages that stratified patients in a stepwise fashion were identified. The corresponding TGM status and plots of overall survival for stages I through IVB are shown in Table 5 and Figure 8. Stages I (<5cm) and II (≥ 5cm) are localized lesions with low histologic grade. Stage III lesions are either high-grade tumors of any size or tumors with regional involvement (contiguous organ invasion or peritoneal implants). Stage IVA refers to patients with systemic metastases or unresectable tumor. Stage IVB is designated when tumor rupture has occurred despite resection of all macroscopic disease. Five-year overall survival rates for stages I, II, III, IVA, and IVB were 75%, 52%, 28%, 12%, and 7%, respectively. Disease-free survivals at 2 years were 89%, 57%, 47%, and 19% for stages I, II, III, and IVB, respectively.

TABLE 4. *Univariate Analysis of Factors That Influence Overall Survival for Each Site of Primary Tumor*

	Stomach			Small Bowel			Large Bowel		
Prognostic Factor	Evaluable Patients (n)	Median (mo)	p*	Evaluable Patients (n)	Median (mo)	p*	Evaluable Patients (n)	Median (mo)	p*
Type of operation			0.002			0.0001			0.007
Complete resections, no rupture	(44)	41		(44)	48		(14)	75	
Incomplete resections	(21)	16		(18)	24		(4)	24	
Complete resection, rupture	(5)	11		(12)	19		(2)	12	
Extent of disease			0.003			0.04			0.05
Localized	(35)	46		(45)	42		(10)	76	
Contiguous organ	(8)	29		(40)	40		(4)	36	
Implants resectable	(7)	15		(29)	29		(3)	14	
Implants unresectable	(2)	20		(4)	30		(0)	—	
Metastases	(17)	15		(13)	22		(4)	24	
Tumor size (cm)			0.05			0.9			0.04
<5	(4)	120+		(4)	45		(4)	104	
5–10	(14)	26		(21)	29		(5)	71	
>10	(38)	25		(35)	32		(9)	23	
Tumor grade			0.07			0.3			0.7
Low	(11)	56		(23)	39		(4)	71	
High	(29)	29		(21)	46		(10)	41	
Type of primary organ resection†			0.26			0.87			(—)‡
Wedge resection	(8)	67		(7)	75				
Bowel resection	(22)	47		(26)	49				
Adjacent organs resected†			0.65			0.56			(—)‡
None	(23)	55		(31)	50				
Yes	(7)	41		(3)	45				

* p value from comparison of survival by Lee-Desu statistic.

† Only localized tumors with complete resections without tumor rupture were compared.

‡ Variable not evaluated.

Discussion

Gastrointestinal leiomyosarcomas occur infrequently, accounting for only 0.1% to 3% of all gastrointestinal malignancies. Approximately 150 new cases are diagnosed annually in the United States.[6] Furthermore, a significant proportion of patients—90% in one series[7]—have their tumors discovered at operation without prior diagnosis

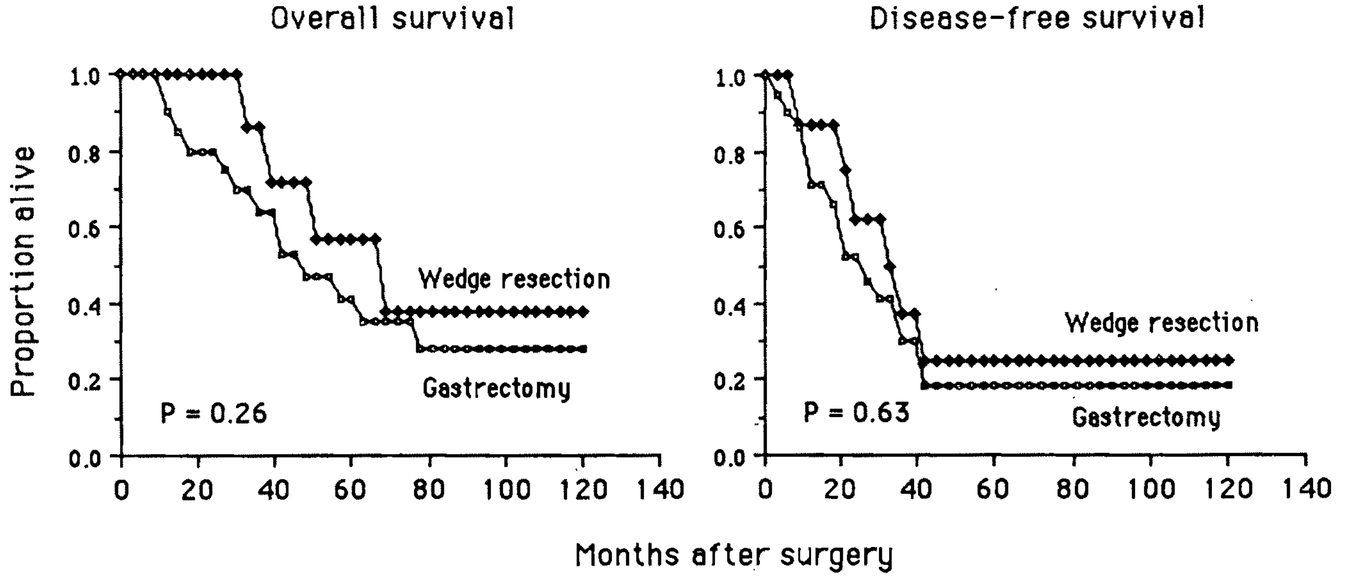

FIG. 6. Influence of wedge resection *vs.* gastrectomy for leiomyosarcomas localized to the stomach on overall and disease-free survival rates. Wedge resection (n = 8); gastrectomy (n = 22).

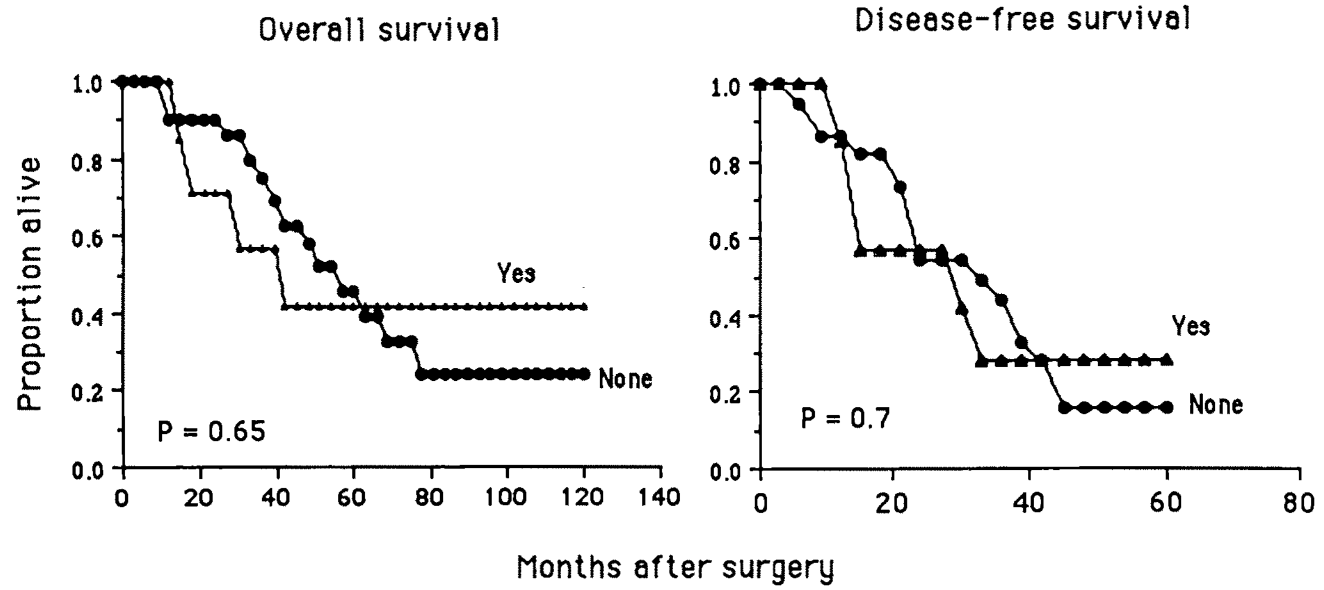

FIG. 7. Influence of resecting adjacent organs for localized leiomyosarcomas of the stomach on overall and disease-free survival rates. Resection (n = 7); no resection (n = 23).

when they present with bleeding, perforation, or obstruction. Thus, the surgeon is required to formulate adequate therapy, usually in an acute situation, for an exceedingly rare disease. Unfortunately, information regarding appropriate surgical management options and their corresponding outcomes remains scarce. The purpose of this study was to evaluate the influence of various clinicopathologic factors, including type of surgical resection, on overall and disease-free survival. From these results, the influence of surgically related procedures on outcome for both localized and invasive lesions could be clarified and appropriate therapeutic options formulated. Additionally, a staging classification incorporating significant prognostic factors was evolved. The ability of such a staging classification to stratify patients into prognostic groups for overall and disease-free survival was examined.

Overall survival at 5 years for patients with gastrointestinal leiomyosarcomas has been reported to be as high as 50%, whereas a considerable range (25% to 50%) exists from various series.[6] In this study, actuarial survival for all patients was only 28%. This finding is in agreement with Akwari et al.[8] and indicates that with adequate long-term follow-up, a high incidence of recurrences and subsequent fatalities can be anticipated. Only 10% of patients remained free of disease as of the last follow-up visit. The clinicopathologic features of this study cohort are comparable to those of other published series[9-14] and suggest that our sample population may be representative of the general population.

As has also been indicated by these reports,[9-15] variables such as tumor size, grade, completeness of tumor resection, and extent of the spread of disease are useful in pre-

TABLE 5. *Overall and Disease-Free Survival Based on M. D. Anderson Cancer Center Staging Classification for Gastrointestinal Leiomyosarcoma*

			Overall Survival (yr)			Disease-free Survival (yr)	
Stage	TGM	N (%)	5	8	10	2	4
I	T1 G1 M0	10 (7)	75%	56%	28%	89%	28%
II	T2 G1 M0	12 (9)	52%	28%	28%	57%	34%
III	T1–2 G2 M0 T3 any G M0	47 (34)	28%	14%	14%	47%	18%
IVA	M1 or residual disease after surgery	46 (33)	12%	4%	0%	—	—
IVB	T4	24 (17)	7%	—	—	19%	19%

Staging classification involving 139 patients for overall survival and 93 patients for disease-free survival.

T, tumor size and extra-organ involvement: T1 = localized; <5 cm; T2 = localized, ≥5 cm; T3 = contiguous organ invasion or peritoneal implants, any size; T4 = tumor ruptured, any size. G, tumor grade: G1 = low grade; G2 = high grade. M, distant metastases: M0 = no metastases; M1 = metastases present.

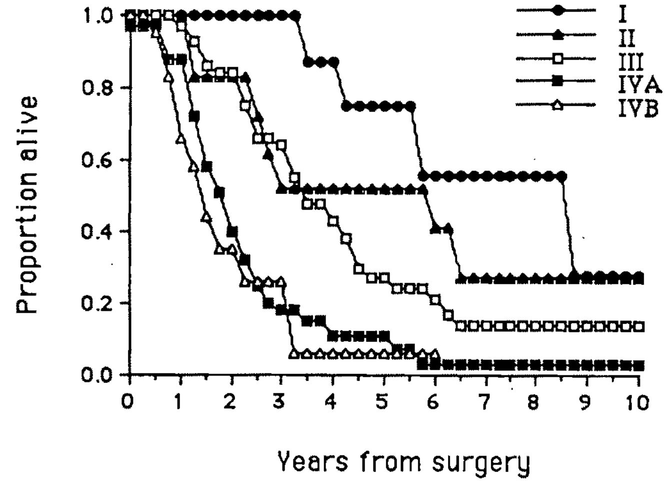

FIG. 8. Overall survival by staging of disease based on M. D. Anderson Staging Classification. Criteria and sample size for each stage are shown in Table 5.

dicting outcome of patients. Nevertheless, type of operation was identified as the only prognostic factor of significance via regression analysis in this study. Such findings underscore the central role of surgery in gastrointestinal leiomyosarcomas and emphasize that extirpative procedures with curative intent should be attempted for tumors invading adjacent organs or with associated peritoneal seeding. Removal of all gross disease improves outcome even in such patients with advanced disease. Thus, survival of patients with contiguous organ involvement or peritoneal implants was not significantly different compared with patients with localized lesions, provided all tumor was surgically excised. For *localized* lesions in the stomach or small bowel, wedge resection of the primary organ appears to be adequate, if all gross disease is removed. Wedge resections resulted in similar overall and disease-free survivals compared with gastrectomies or formal bowel resections. Similarly, resecting adjacent organs did not improve overall and disease-free survival. These results indicate that tumor spread either via mucosal extension or submucosal lymphatics is clinically less significant when compared with other routes of dissemination. This extrapolation is supported by the infrequent spread to regional lymph nodes (0% to 15%) from gastrointestinal sarcomas.[7,16,17] Thus, regional lymphadenectomy, as has been proposed by others,[16] would presumably not result in beneficial effects, particularly because the majority of patients present with systemic metastases as their first site of failure.[18]

Tumor rupture, either spontaneously or iatrogenically, was associated with an adverse influence on both overall and disease-free survival. Despite removal of all macroscopic tumor, affected patients are at extreme risk for early recurrences. A number of mechanisms may explain these observations. Tumors that are susceptible to rupture, presumably because of a large necrotic component, also may be inherently aggressive in their biologic behavior. Alternatively, the dissemination of tumor cells at the time of rupture, apart from seeding potential implants in the peritoneal cavity and the liver, also could lead to host immune suppression and result in an increase in tumor proliferative activity and appearance of recurrent disease. Although the mechanisms involved remain speculative, it is clear from the data that a grave prognosis can be anticipated in patients with gross spillage of tumor.

The grade of tumor has been shown to be of prognostic significance for survival.[8-15] In this study, tumors were not graded by an individual review and are therefore representative of the overall expertise of pathologists in a tertiary cancer center. As alluded to by Appelman,[19] the criteria for such grading are not rigidly defined; considerable subjectivity exists in their application. Morphologic criteria include cellularity, vascularity, amount of stroma, and number of mitotic figures, etc. Despite these limitations, grade of lesion was significantly related to disease-free survival and overall survival after complete resection of primary tumor. Patients with high-grade tumors, despite initial "curative surgery," are at higher risk for recurrences and are associated with a poor clinical outcome.

The analysis of prognostic factors based on tumors arising from different sites, as shown in Table 4, emphasizes the applicability of type of operation and extent of disease as important determinants irrespective of the primary site of origin. These results also support the feasibility of a staging classification suitable for all leiomyosarcomas arising from the gastrointestinal tract. The proposed staging classification may be useful in predicting prognosis and recommending adjuvant therapy for individual patients at high risk of relapse.

In conclusion, type of operation is the most important determinant of overall survival in patients with gastrointestinal leiomyosarcomas. Surgery remains the primary modality of treatment and extirpation of all macroscopic disease without gross spillage should be the goal of therapy. In patients with locally advanced disease, resection of peritoneal implants or contiguous organs invaded by the primary tumor should be attempted because survival is improved when complete resection of the primary tumor without rupture is performed. For localized lesions, removal of all macroscopic disease by wedge excision appears adequate because the addition of more extensive resection of either the primary organ or adjacent organs did not further increase survival. Despite such "curative surgery," the majority of patients will develop recurrent disease. Thus, the development of more effective multimodality adjuvant approaches is required to further improve survival for patients with gastrointestinal leiomyosarcomas.

Acknowledgments

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The Efficacy of Gallium Scintigraphy in Detecting Malignant Soft Tissue Neoplasms

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A prospective study was conducted on 55 consecutive patients to evaluate the efficacy of gallium scintigraphy in detecting malignancy in any soft tissue mass. It was determined that gallium scintigraphy could detect malignancy with a sensitivity of 96% and a specificity of 87%. Large and small sarcomas, irrespective of their fascial location, were identifiable by gallium imaging. Occult, nonpulmonary sites of disseminated disease were detected in 13%. Gallium scintigraphy proved to be a reliable predictor of malignancy for all soft tissue masses, but because of its cost, it must be used judiciously.

GALLIUM-67 (^{67}Ga) citrate scintigraphy alone or in combination with technetium-99 diphosphonate bone scintigraphy, has proved useful in the staging of soft tissue sarcomas of the extremities.[1-4] Three retrospective studies have reported a combined 83% sensitivity for this modality in diagnosing the malignancy of a soft tissue mass. The single prospective report of the utility of gallium scintigraphy in evaluating soft tissue masses calculated a 72% sarcoma specificity.[4] This analysis considered only masses that were large (5 cm or greater in diameter), located beneath the deep fascia, or possible local recurrences. These four studies shared in common a population of patients whose diagnosis of soft tissue sarcoma was almost certain.

Many individuals are referred to a surgical oncologist for the evaluation of a symptomatic mass that is less than 5 cm in diameter or located within the subcutaneous tissue. Many have masses that may not be malignant and would benefit by that prebiopsy knowledge. Therefore, a prospective study was undertaken to report the predictive value of gallium imaging in detecting malignancy for all isolated soft tissue masses presenting to a musculoskeletal oncologist over a 2-year period.

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Materials and Methods

Population

Sixty-seven consecutive patients were referred with an isolated soft tissue mass larger than 1 inch (2.5 cm) in diameter, extra-articular in location, situated either beneath or superficial to the deep fasica, and having no previous history of neoplasm to rule out malignancy. Clinically obvious cases of infection, ganglions, or non-neoplastic entities were not included in the study as determined by careful examination. No individual with a suspected tumor recurrence or a biopsy within 2 weeks before scintigraphy was included.[4]

Twelve patients were excluded from final review for failure to meet all criteria (3), or because excisional biopsies before referral left either microscopic or no residual disease (9), as determined postoperatively. The cohort population consisted of 55 patients. The patients ranged in age from 9 to 90 years, with a median age of 50 years. There were 21 men and boys and 34 women and girls in the study group. All masses were anatomically located in the extremities (45 patients) or limb girdles (10 patients).

Radiopharmaceutical

Gallium-67 citrate is cyclotron produced and emits radiation over a broad energy range from 93 to 880 KeV. The principal energy peaks are at 93, 188, 296, and 388 KeV. Normally, ^{67}Ga accumulates in the liver, spleen, and colon, with small amounts in the skeleton and bone marrow. Normal activity is seen in the nasopharynx, lacrimal glands, salivary glands, and external genitalia. Uptake may be noted in breasts during pregnancy, lactation, and after exogenous estrogen administration. Renal ex-

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cretion is the predominant mechanism of elimination and after exogenous estrogen administration. Renal ex-during the first 24 hours; therefore, symmetric visualization of kidneys in the 24-hour scan is not unusual.

The exact mechanism of gallium localization in tumors and inflammatory lesions is unclear; however, reports demonstrate accumulation in lysosomal-like granules within viable cells.[5] Subsequently, ^{67}Ga was found to bind to human lactoferrin and transferrin on the surface of granulocytes and lymphocytes but not on red blood cells.[6,7]

The adult dosage of ^{67}Ga was 45 μCi per kilogram of body weight. Pediatric dosage ranged from 45 to 90 μCi/kg as determined by the radiologist. If turbidity was noted in the vial, the radiopharmaceutical was discarded. Gallium citrate was acquired from E.I. Dupont de Nemours and Co. (Billerica, MA 01862).

Gallium-67 was administered intravenously over 3 minutes. The time interval between administration and early scanning was 24 to 48 hours, and late scanning, 72 hours. Patients were asked to empty their bladders before scanning, and, in addition to orally administered castor oil and a Clysodrast (Armour Pharmaceutical, Blue Bell, PA) enema, additional enemas were frequently given if images were obscured because of bowel contents. Gallium scintigraphy was routinely performed as part of the staging workup for all patients with a soft tissue mass thought to be malignant.

Imaging

At our facility, Vanderbilt University Medical Center (VUMC), scintigrams were obtained on the Siemens "Digitrac" large field of view camera (Siemens Gammasonics, Inc., 2501 Barrington Road, Hoffman Estates, IL 60195), which was fitted with a 15-inch diameter crystal and medium energy collimators. The scanner used three-pulse height analyzers to correspond to the three major photoenergy peaks. Static images of 1,000,000 counts of radiation per image were obtained in anteroposterior and lateral projections while the patient was supine on a Plexiglas table. The scanner's resolution capability included lesions 1 cm in size or larger.

The scintigraphic images were interpreted by one of three independent nuclear medicine specialists who had no knowledge of the cases except that a mass was present in each. Final assignment of scintigraphic intensity score was determined by one of the authors (HSS), who used the scale based on Kirchner and Simon.[4] Any abnormal area of uptake was compared relative to liver intensity: 4+ > liver, 3+ = liver, 2+ > adjacent tissue but < liver, 1+ equivocal, 0 = no uptake.

Results

All 55 patients had definitive resection to ascertain the true pathologic diagnosis and correlate the size and location of the tumor. All gallium scans were available for review. The working hypothesis assumed that increased scintigraphic activity signified malignancy. There were no complications associated with ^{67}Ga citrate administration or imaging.

Only six soft tissue masses were smaller than 5 cm in diameter and greater than 2.5 cm. These were a hemangioma, angiosarcoma, adenoma, malignant fibrous histiocytoma (MFH), epithelioid sarcoma, and neurilemoma. The neurilemoma and epithelioid sarcoma were located beneath the deep fascia. Therefore, there were three malignant neoplasms in this study that were smaller than 5 cm in diameter. The MFH and epithelioid sarcoma were gallium positive.

Seven of forty-nine masses were 5 cm or greater in diameter at the time of gallium imaging and were located in the subcutaneous tissue. Three of the six represented malignant pathologies (MFH, angiosarcoma, and non-Hodgkin's lymphoma). Table 1 delineates the diagnoses, patient number, scintigraphic intensity, and location of the soft tissue masses in the study population. Table 2 outlines the location and size distribution of the 55 primary soft tissue masses studied.

There were four false-positive scintigraphic results detected when comparing the scan with the primary site of pathology. Neurofibroma, hemangioma, toxoplasmosis, and myositis constituted the diagnoses of false-positive images.

One false-positive result was detected relative to a nonprimary site of scintigraphic abnormality. In this case, a patient had a gallium-positive liposarcoma in the anterior compartment of the thigh and a concurrent, contralateral scintigraphically positive adrenal. Two computed tomography (CT)-directed needle biopsies of the adrenal proved negative for any neoplasm. One year of image follow-up has not shown any change in the size of the adrenal.

A single false-negative gallium scan of the primary soft tissue mass was detected in this study. A subcutaneous high-grade angiosarcoma, 3 cm in diameter, was resected from the mid-distal calf of a 73-year-old woman, whose primary tumor site was gallium negative. Interestingly, an ipsilateral external iliac lymph node detected as positive on the scintigram, and not palpable on examination of this obese woman, was identified. Open biopsy of this node confirmed the diagnosis of regionally metastatic angiosarcoma (Fig. 1).

The sensitivity, specificity, and positive predictive value of gallium scintigraphy in detecting malignancy of masses in the soft tissues was 96%, 87%, and 85%, respectively.

TABLE 1. *Staging Analysis by Gallium Scintigraphy in 55 Patients*

		Scintigraphic Results*		Fascia	
Histogenesis	No. of Patients	Primary	Metastases	Deep	Subcutaneous
Malignant fibrous histiocytoma	7	2+		5	2
Liposarcoma	4	2+	2 + (N = 1, S = 1)†	4	0
Non-Hodgkin's lymphoma	4	3+	3 + (N = 4, S = 8)	3	1
Fibrosarcoma	2	2+		2	0
Synovial sarcoma	2	2+	2 + (N = 1, S = 1)	2	0
Angiosarcoma	2	1+‡	2 + (N = 2, S = 3)	0	2
Other malignancies§	3	2+		3	0
Lipoma	8	0		6	2
Hemangioma	5	trace†		4	1
Myxoma	2	0		2	0
Other benign‖	6	trace†		5	1
Infection	1	4+		1	0
Nonneoplastic¶	9	trace†		7	2

* Average intensity.

† Noninfectious false-positive result.

‡ False-negative result.

§ One each: epitheloid sarcoma, hemangiopericytoma, and adenocarcinoma.

‖ One each: desmoid, neurilemoma, neurofibroma, benign fibrous histiocytoma, adenoma, and chondroma.

¶ Three ganglion cysts, two hematomas and lipodystrophies, one myositis and cystic hygroma.

N, no of patients; S, no. of nonpulmonary metastatic sites detected by gallium scintigraphy.

Discounting the single case of toxoplasmosis infection, gallium scintigraphy yielded a specificity of 90%. Thirteen nonpulmonary sites of increased gallium uptake were detected in eight patients. Seven patients had a true positive gallium study for nonpulmonary distant disease, confirmed by needle biopsy. Thus, seven of 55, or 13%, of individuals had their clinical tumor stage altered because of the results of gallium scintigraphy.

Non-Hodgkin's lymphoma was the single neoplasm most consistently gallium intense (Fig. 2). Other neoplasms, irrespective of whether they were the primary or secondary sites, had no characteristic radiointensity. Position relative to the deep fascia or anatomic location of the mass did not appear to directly influence the uptake of radioisotope by the neoplasm.

Discussion

A prospective study was conducted to evaluate the efficacy of gallium scintigraphy in differentiating benign from malignant soft tissue masses irrespective of size and location relative to the deep fascia. It was determined that gallium scintigraphy could detect malignancy with a sensitivity of 96% and a specificity of 87%. A range of histologies, sizes, and mass locations were examined as presenting to a referral center over a 2 period. Obviously non-neoplastic cases were not included in the study group. This study differs from others previously reported in that it is prospective and includes clinically suspicious superficial masses that are less than 5 cm in diameter and larger than 2.5 cm.

The results indicate that gallium scintigraphy is quite accurate in predicting whether or not a soft tissue mass is malignant. Additionally, this study corroborated the findings of Finn et al.[2] that gallium scintigraphy is capable of detecting nonpulmonary sites of disseminated disease. This occurred in 13% of patients. Gallium scintigraphy proved to be an important imaging modality for the accurate staging of soft tissue sarcomas and non-Hodgkin's lymphomas.

The cost of radiopharmaceuticals was $188.50 per dose. A whole body scan for an outpatient examination was $353.70 *versus* $442.15 for inpatients. The nuclear medicine radiologists' interpretation fee was $104.50. The total fees/costs ranged from $646.70 for an outpatient study to $735.15 for inpatients. Thus, a gallium scan is expensive and it must be used judiciously.

Gallium scintigraphy is sensitive in detecting soft tissue sarcomas, but not quite as specific because of its uptake in inflammatory lesions. Thus, any soft tissue mass that is gallium positive must include infection, benign inflammatory lesions, lymphoma, and sarcoma in the differential

TABLE 2. *Location and Size Distribution of Soft Tissue Masses*

Fascial Location	Small (2.5 cm < x <5 cm)	Large (x ≥5 cm)	Total
Subcutaneous	4	7	11
Deep	2	42	44
Total	6	49	55

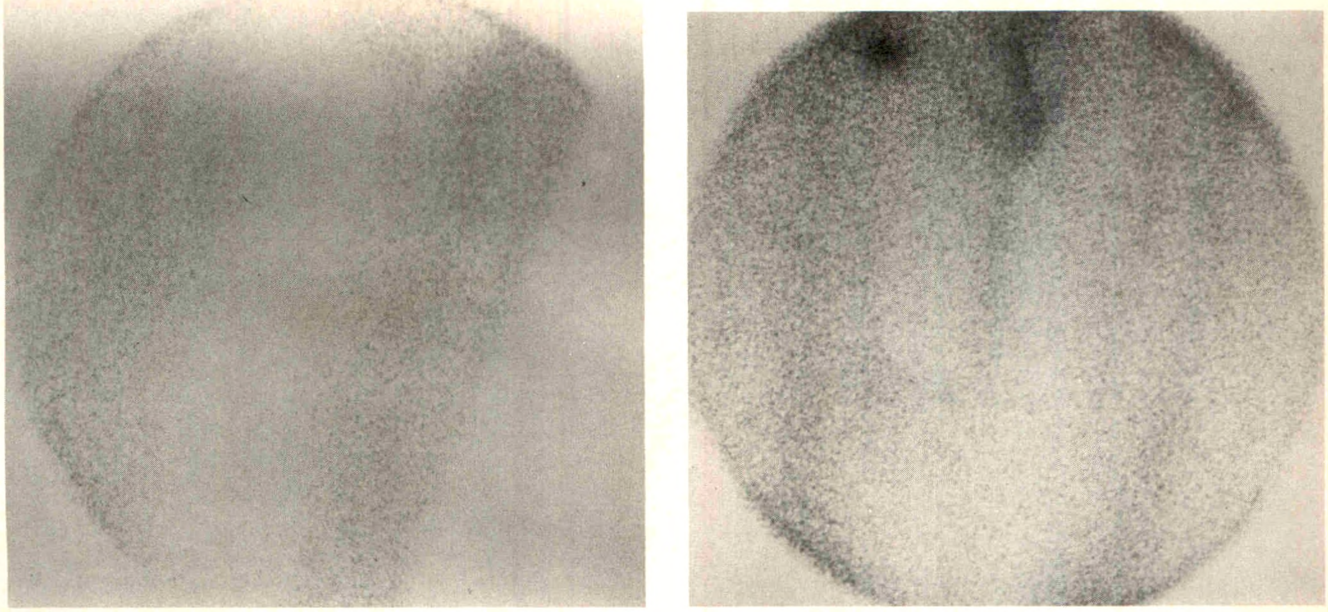

FIG. 1. ^{67}Ga citrate scintigram at 72 hours in a patient with a primary angiosarcoma located subcutaneously in the mid-distal calf. (A, left) Lateral view of the involved calf. False-negative scan of a 3-cm-diameter lesion. (B, right) Frontal view of thighs and inferior pelvis. True-positive scan reflecting regional metastasis to an ipsilateral external iliac lymph node.

diagnosis. The specificity of gallium imaging for soft tissue malignancy approaches 90% only in a carefully scrutinized patient population, such as that of a musculoskeletal oncologist, where infections and many non-neoplastic lesions can be excluded clinically.

The sensitivity of gallium scintigraphy for detecting small soft tissue sarcomas has been questioned. Four of seven normal gallium scintigrams were noted in patients who had tumors less than 5 cm in diameter in one retrospective study.[2] Kaufman suggested that tumors smaller than 2 cm in diameter can have false-negative gallium scans.[4] This study determined that two of three small (less than 5 cm in diameter) soft tissue sarcomas had true-positive gallium scans. We are unable to explain the only false-negative scintigram in a patient with angiosarcoma, except that fortuitously this same patient had a positive scintigram for ipsilateral external iliac lymph node metastasis. Earlier studies performed gallium scintigraphy with a rectilinear scanner, which has been replaced with recent versions of the gamma camera. Improved instrumentation has increased the sensitivity of gallium imaging.

In conclusion, gallium scintigraphy proved to be a reliable predictor of malignancy for all soft tissue masses. Discounting clinically detectable cases of infection, it has a sensitivity and specificity approximating 90% for detecting soft tissue malignancies. No morbidity was associated with radioisotope administration in this study; however, the cost to the health care system approaches $1000 per individual examination. Clearly, gallium imaging should not be ordered for every suspicious soft tissue mass detected by the inexperienced examiner. A thorough clinical examination by a physician familiar with managing neoplasms of the musculoskeletal system can identify a small population of individuals likely to harbor a malignancy. Gallium scintigraphy can serve at least two important roles in this situation. It can preoperatively aid

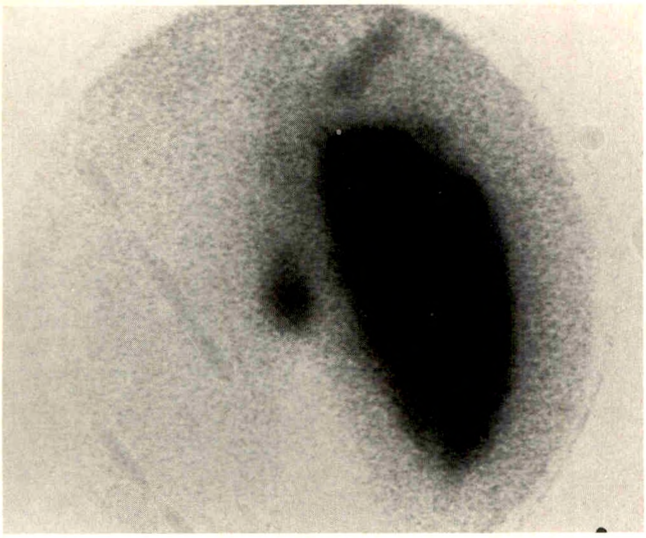

FIG. 2. ^{67}Ga citrate scintigram at 72 hours in a patient with non-Hodgkin's lymphoma. A large quadriceps neoplasm is shown with an ipsilateral testicular site of tumor. Note the extreme gallium intensity of this specific neoplasm.

in differentiating benign from malignant neoplasms and thus may offer the patient a conservative treatment option. Additionally, gallium scintigraphy can be used to accurately stage disease extent in soft tissue sarcomas because of its ability to detect occult nonpulmonary metastases. Gallium scintigraphy also may prove to have an important role in the long-term evaluation of individuals with the potential of tumor recurrence after initial soft tissue sarcoma management.

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Flow Volume Loops in Patients With Goiters

JAMES G. GERAGHTY, M.CH., F.R.C.S.I., EAMONN C. COVENEY, M.B.,
MICHAEL KIERNAN, and NIALL J. O'HIGGINS, M.D., F.R.C.S.I.

Plain radiology is the standard means of assessing upper airway obstruction in patients with goiters. Flow volume loop curves will provide additional information, because they allow a quantitative assessment of airflow dynamics in the respiratory cycle. Fifty-one patients had flow volume loops performed before and after thyroidectomy. There was a significant increase in the maximum inspiratory flow rate (3.9 ± 0.2 *versus* 4.9 ± 0.2 L/second, $p < 0.01$) after thyroidectomy. Eight of twelve patients with normal tracheal radiology had improved airflow dynamics in the postoperative period. The flow volume loop curve is a simple noninvasive means of assessing airflow dynamics in patients with goiters and may be superior to conventional radiology.

UPPER RESPIRATORY TRACT obstruction is a well-recognized complication of thyroid disease and up to 45% of patients with goiters have symptoms suggestive of upper airway obstruction.[1] Plain radiology of the thoracic inlet is the standard way of identifying this complication. This investigation, however, provides a static measurement only of the upper respiratory tract and gives no information on airflow dynamics in the upper respiratory tree.

Flow volume loop curves are a simple noninvasive method of assessing upper airway obstruction.[2] They provide a quantitative assessment of airflow in both inspiratory and expiratory phases of the respiratory cycle, and the shape of the flow volume loop curve can also identify the site of upper airway obstruction. This study evaluates the use of flow volume loops in patients with goiters and compares conventional radiology with the flow volume loop curve in the detection of upper respiratory tract obstruction.

From the University Department of Surgery, St. Vincent's Hospital, Dublin, Ireland

Materials and Methods

Patients

A total of 51 patients undergoing thyroidectomy in the period 1986 to 1989 were entered into the trial. The mean age was 49 years (range, 18 to 76 years) and the male: female ratio was 8:1. Patients with a history of ischemic heart disease, asthma, or chronic obstructive airways disease were excluded from the trial. All patients had indirect laryngoscopy performed preoperatively, and the vocal cords also were examined at extubation after thyroidectomy. Symptoms of upper airway obstruction were documented preoperatively and 1 month after surgery. Thoracic inlet x-rays (anteroposterior and lateral) were performed before surgery. The type of surgery carried out and histology of the resected gland are shown in Table 1. All patients had cervical goiters alone on clinical examination, and four patients had minimal retrosternal extension at surgery.

Flow Volume Loop Curves

Preoperative flow volume loop curves were performed at admission for thyroidectomy, and postoperative values were obtained a minimum of 4 weeks after surgery. Flow volume loop curves were constructed as described by Miller and Hyatt.[3] Each patient performed a maximal forced expiratory maneuver followed by forced inspiration, which was recorded using a Fleish type pneumotach (Vitalograph/Compact, Buckingham, UK). The respiratory maneuver was recorded by a sensitive pressure transducer that produced an electrical signal. A microprocessor computed the data and displayed the results on a screen.

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Accepted for publication May 31, 1991.

TABLE 1. *Type of Surgery and Histologic Findings*

Variable	No. of Patients
Operation (n = 51)	
Lobectomy and isthmusectomy	35
Subtotal thyroidectomy	14
Total thyroidectomy	2
Histologic findings	
Multinodular goiter	24
Adenoma	14
Graves' disease	8
Cancer	5

These then were printed on electrosensitive paper for a permanent record (Fig. 1). All flow volume loop curves were supervised by one technician well versed in the technique. A minimum of three respiratory maneuvers were performed, and the maximum respiratory effort was recorded. The criteria selected by the American Thoracic Society (ATS) were used to select the Best Test automatically. The ATS criteria specifies that the two Best Tests should be within 5% of each other,[4] and only flow rate volumes that conformed with this specification were included in the study.

Statistical Analysis

Results are presented as mean plus or minus standard error of the mean (mean ± SEM). Pearson's correlation coefficient and Student's t test were used for data analysis.

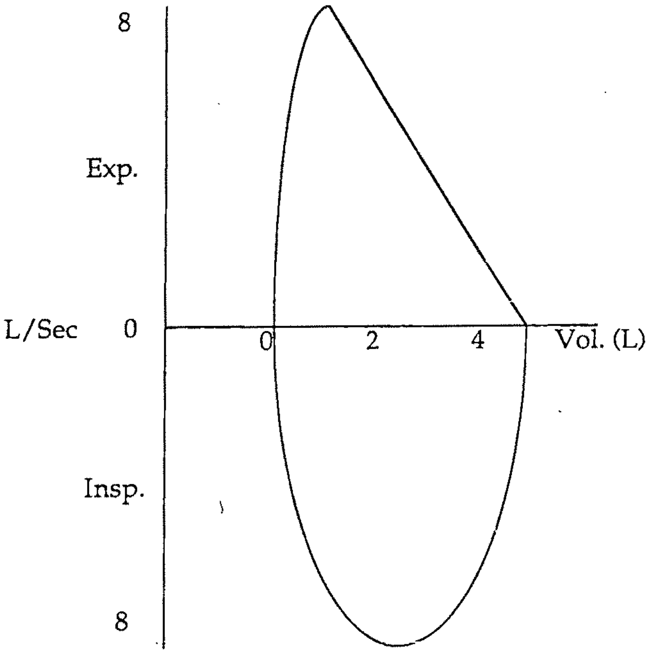

FIG. 1. Normal flow volume loop curve showing the inspiratory and expiratory phases of the respiratory cycle.

TABLE 2. *Respiratory Flow Rates in Goiters Before and After Operation*

	Before Operation	After Operation
Maximum inspiratory flow rate (L/sec)	3.9 ± 0.2	4.9 ± 0.2*
Inspiratory V_{max} 50 (L)	3.7 ± 0.2	4.7 ± 0.2*
Maximum expiratory flow rate (L/sec)	5.4 ± 0.3	6.3 ± 0.3†
Expiratory V_{max} 50 (L)	3.8 ± 0.2	4.1 ± 0.2

Mean ± SEM.
* $p < 0.01$.
† $p < 0.05$.

Results

Flow Volume Loop Curves

There was a significant improvement in the maximum inspiratory flow rate and the inspiratory $V_{max}50$ in patients after thyroidectomy (Table 2). This improvement, however, was less marked in the expiratory phase of the flow

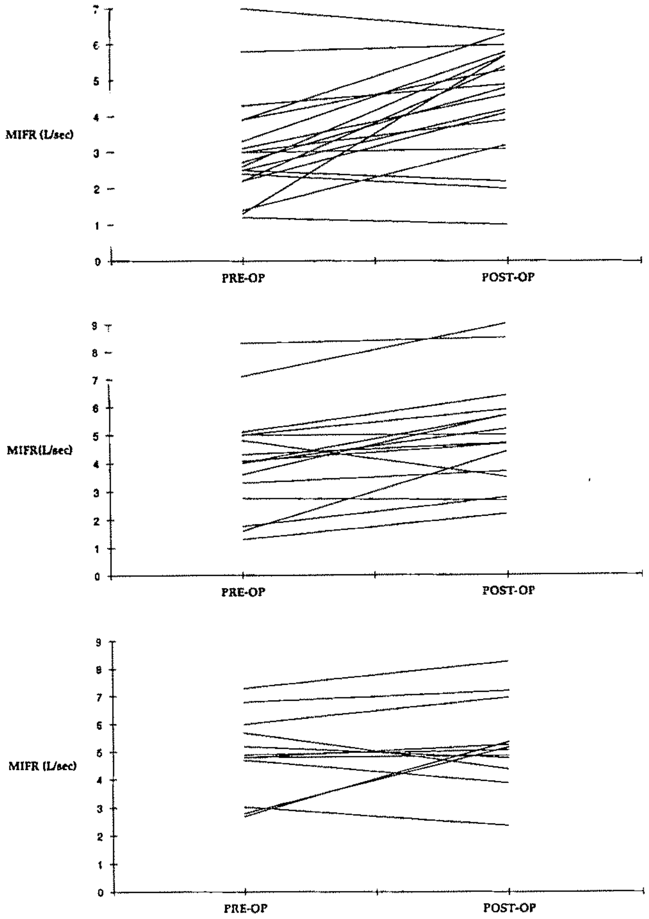

FIG. 2. Individual values for maximum inspiratory flow rates before and after operation in patients with (A, top) tracheal narrowing, (B, center) tracheal deviation, and (C, bottom) normal tracheal radiology.

volume loop (Table 2). Thoracic inlet studies were available on 50 patients and divided into three separate groups to allow comparison with the flow volume loop curves.

In group A, the trachea was narrowed (n = 21); in group B the trachea was deviated but not narrowed (n = 17); and in group C the trachea was normal (n = 12).

There was a significant increase in the mean maximum inspiratory flow rate postoperatively in patients in group A (Fig. 2A, $p < 0.05$). There was also an increase in the maximum inspiratory flow rate in patients in groups B and C (Fig. 2B, C), but this was not statistically significant.

The mean weight of gland resected was 113 g (range, 14 to 700). There was no correlation between the weight of thyroid gland removed and the change in the maximum inspiratory flow rate postoperatively ($r = 0.25$, p = not significant [NS]). There was also no correlation between the weight of gland removed and other variables of the flow volume loop.

Symptoms of Airway Obstruction

The change in the maximum inspiratory flow rate (ΔMIFR) in asymptomatic and symptomatic patients in the three groups is given in Figure 3. There was no significant difference in the ΔMIFR between symptomatic and asymptomatic patients in groups B and C (Fig. 3B and C). There was a significant increase in the ΔMIFR in symptomatic patients with tracheal narrowing when compared with those with no symptoms (0.58 *versus* 1.63 L/mm, $p = 0.05$).

Discussion

The results of this study show that thyroidectomy is associated with an overall improvement in airflow dynamics postoperatively that occurs principally in the inspiratory phase of the flow volume loop curve. This finding is also in agreement with the fact that most patients studied had cervical goiters with minimal retrosternal extension, and this flow volume loop pattern has been reported previously by Miller and Hyatt.[3]

Plain radiology of the upper airways is the most commonly used investigation to detect upper airway obstruction. The present study compared the use of flow volume loop curves and standard thoracic inlet studies in assessing upper respiratory obstruction. Patients with tracheal narrowing had the greatest improvement in both the maximum inspiratory flow rate and the inspiratory $V_{max}50$ in the post operative period, whereas postoperative flow volume loop curves improved to a lesser extent in patients with tracheal deviation alone. This study demonstrated an improvement in postoperative flow volume loop curves

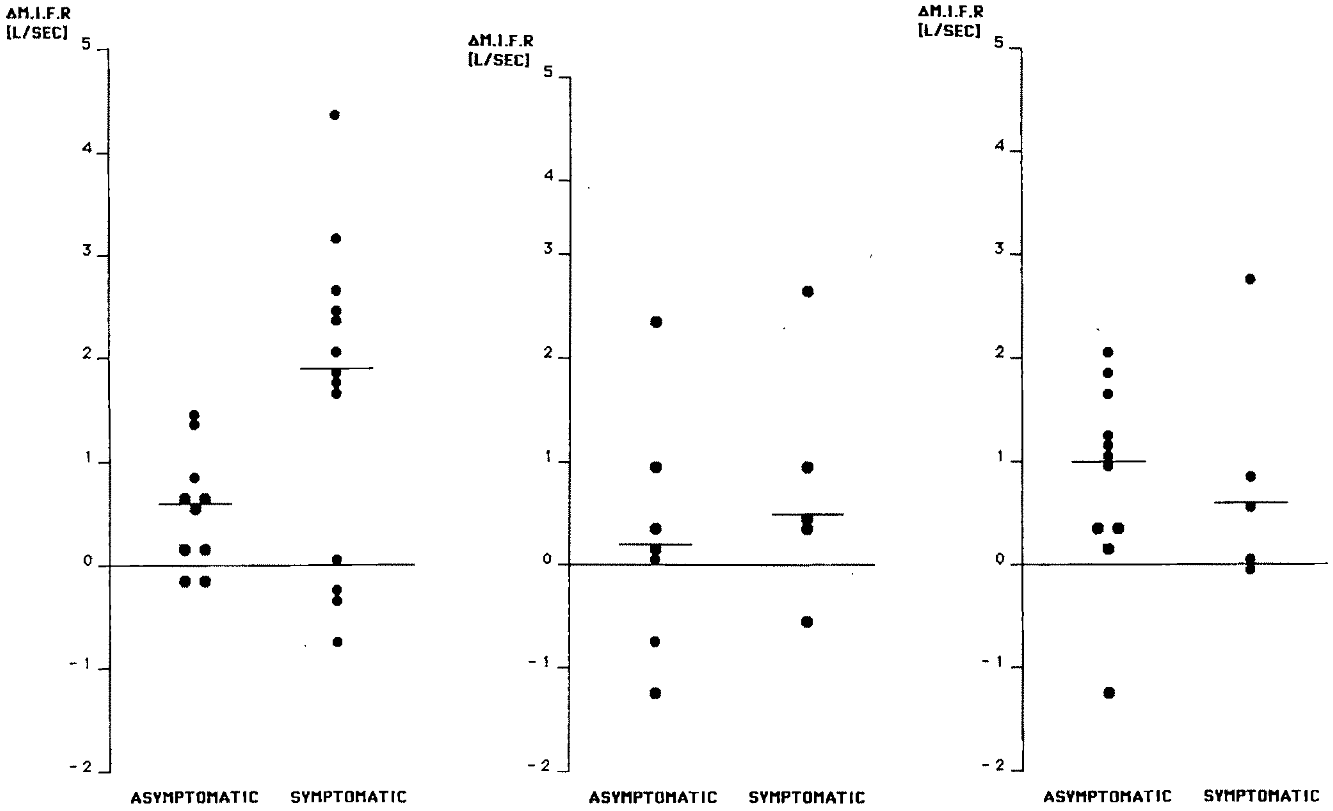

FIG. 3. Change in the maximum inspiratory flow rate (ΔMIFR) in symptomatic and asymptomatic patients with (A, left) tracheal narrowing ($p < 0.05$), (B, center) tracheal deviation (p = NS), and (C, right) normal tracheal radiology (p = NS).

in patients with normal tracheal radiology, although this did not reach statistical significance. This result suggests that normal tracheal radiology does not exclude the presence of abnormal upper airway dynamics and that flow volume loops may be a more sensitive method of detecting upper airway obstruction in this patient population. This finding is in agreement with that of Jauregui et al.,[1] who showed that flow volume loops confer additional advantage on conventional radiology alone in the diagnosis of upper airway abnormalities. This study also shows that plain x-rays remain an important aid to diagnosis because those patients with symptoms and tracheal narrowing were the only group to show a significant increase in the postoperative maximum inspiratory flow rate.

Flow volume loops have been used primarily to detect upper airway dynamics in patients with asthma or chronic obstructive airways disease.[2,5] They are now being used with increasing frequency to diagnose upper airway obstruction in patients with goiters.[6] Miller and Hyatt[3] used flow volume loops to quantify abnormal airflow dynamics due to strictures of the trachea and and underlined the importance of the contour of the loop in identifying the site of airway obstruction. Jauregui and colleagues[1] demonstrated that 60% of their patients with goiters had upper airway obstruction detected by flow volume loop curves and that medical management was associated with a reduction in the size of the goiter and an improvement in the flow volume loop. The volume of the thyroid gland in that study was assessed clinically, however, and not by conventional radiology. In a larger series, Miller and associates[6] showed that 31% of patients with goiters had flow volume loop detected upper airway obstruction and that thyroidectomy was successful in improving the postoperative flow volume loop in over 90% of patients. This improvement is higher than that reported in the present study. This discrepancy can be explained by the fact that only four patients in the present study had retrosternal extension, whereas that reported by Miller et al.[6] had retrosternal extension in half of their patients undergoing thyroidectomy. The present study therefore suggests that the prevalence of abnormal upper airway dynamics in patients with cervical goiters may be higher than previously reported. One interesting finding in this study was the lack of correlation between the change in the postoperative flow volume loop values and the weight of gland resected. This result suggests that the size of the gland does not necessarily correlate with the presence of respiratory obstruction.

A number of different methods have been used to diagnose abnormal airflow dynamics in the respiratory tree, the commonest of which include timed forced expiratory volume and the ratio of forced expiratory volume to the peak expiratory flow rate. There is disagreement concerning the threshold value of the ratio diagnostic of upper airway obstruction,[7] and it has been shown that flow volume loops are superior to this ratio in detecting abnormal airflow dynamics.[6] One source of error associated with the construction of flow volume loop curves is that they depend on both the effort and cooperation of the patient. It is therefore important that the patient is well instructed before carrying out the respiratory maneuver and that this is performed with maximum effort.[8] To minimize these potential errors, flow volume loops were supervised by one technician, and a minimum of three recordings were taken to obtain the maximum respiratory effort.

The relief of airway obstruction represents an important aspect of surgery for thyroid disease. Flow volume loops are simple to construct and provide a dynamic assessment of upper respiratory airflow. The present study shows that patients with goiters have abnormal airflow dynamics and that flow volume loops are a valuable adjunct to conventional radiology in diagnosing upper respiratory obstruction.

Acknowledgments

The authors thank Adrian Dunne from the Department of Statistics at University College Dublin and Jill Costelo for typing the manuscript.

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LETTERS TO THE EDITOR

December 20, 1990

Dear Editor:

In the November 1990 issue of *Annals of Surgery,* two articles were published supporting the routine use of selective venous sampling for the localization of functioning islet cell tumors of the pancreas.

Dr. Nobin from Sweden, and Dr. Norton from the National Institutes of Health in Bethesda, Maryland, are recognized experts in this field, and their contributions are worthy of study. Although the authors recommend that selective venous sampling should be used in all patients, Norton, in particular, states that intraoperative ultrasonography has been one of the most significant advances in the management of these patients in the past decade. In Norton's series, intraoperative ultrasonography was positive in 10 of 11 patients, in contrast to 9 of 11 for selective venous sampling, and only 5 of 11 for surgical palpation. In Nobin's series, venous sampling was positive in 100% of insulinoma patients in whom the study was performed.

Our group has not embraced selective venous sampling in the evaluation of previously unoperated islet cell tumors, insulinomas, in particular. We continue to believe that the combination of surgical palpation combined with preoperative and intraoperative ultrasonography remains both highly accurate and cost effective (29 of 30 recent patients). We are of the current opinion that, in *most* patients with functioning islet cell tumors, preoperative ultrasonography is the only localizing technique required *if* this can be combined with *experienced* intraoperative palpation of the pancreas and the *routine* use of intraoperative ultrasonography to aid not only in tumor localization, but in demonstration of important pancreatic ductal and vascular anatomy.

JON A. VAN HEERDEN, M.D.
CLIVE S. GRANT, M.D.
Rochester, Minnesota

February 5, 1991

Dear Editor:

One of the purposes of our paper was to show that selective venous sampling in experienced hands may help the surgeon with the diagnosis and localization of endocrine pancreatic tumors. We also stated that selective venous sampling is not necessary in all cases. When clinical, laboratory, and less invasive procedures are conclusive, the selective venous sampling is needless.

Consequently, we agree with Drs. van Heerden and Grant that a less invasive localization technique is preferred, but when there are difficulties, the selective venous sampling is worth using, providing you are familiar with the technique.

We admit that intraoperative palpation and ultrasonography could have been mentioned in the discussion, but our aim was to show what can be obtained by selective venous sampling and not the pros and cons of different procedures.

HANS MÅRTENSSON, M.D., PH.D.
Helsingborg, Sweden

February 15, 1991

Dear Editor:

It is difficult to compare the results of the 30 patients by Drs. van Heerden and Grant in their letter with those in the present study, because in most series up to 80% of insulinomas can be identified preoperatively by angiogram and are usually found by palpation alone at surgery. Our series does not include these patients because all of our patients had negative preoperative imaging studies, and in patients with negative imaging studies, the tumor can be more difficult to find at surgery. We agree with Drs. van Heerden and Grant from the Mayo Clinic that in *most* patients with sporadic insulinoma (non–Multiple Endocrine Neoplasia type 1 patients), the use of preoperative portal venous sampling (PVS) of the portal vein and its tributaries for insulin concentration may not be necessary. Several important facts must be considered, however, before one can totally exclude the use of PVS in these patients and endorse their proposed approach to these patients. First, insulinomas are rare tumors. A recent study from Ireland suggests that the incidence of insulinoma is as low as 0.5 persons per million per year, suggesting that few surgeons will have a large experience with these tumors. Second, unlike gastrinomas that commonly occur in either the duodenum or the pancreatic head (the gastrinoma triangle), insulinomas are uniformly distributed throughout the pancreas. Third, in the 20% of all patients with insulinoma with negative preoperative arteriography, the tumor may be difficult to find. These patients may be more difficult to manage than the vast majority of patients, such as in the Mayo series, who would have had routine preoperative radiographic localization. Fourth, unlike our colleagues, we would never select ultrasound as the only preoperative localizing test for insulinoma because in our experience it only has a 25% true-positive rate compared with arteriography, which has an 80% success rate. Fifth, in our experience and the experience of others, PVS has the greatest ability to provide correct preoperative localizing information and is accurate in between 75% and 100% of patients. Sixth, the medical management of the hypoglycemia in patients with insulinoma is generally not very satisfactory. Finally, because insulinomas in patients with sporadic disease are usually small benign solitary tumors, the goal of surgery is precise intraoperative localization with enucleation of tumor instead of blind resection of normal structures, including possibly duodenum, pancreas, and spleen.

It may be that we would have found all of these tumors with the use of palpation and intraoperative ultrasound (IOUS) without the use of PVS, as van Heerden and Grant suggest, but it does not appear that we would have found all these tumors with only palpation, as Daggett and others have suggested (*Lancet* 1: 483, 1981). Because of the frequent unsatisfactoriness of medical management for long-term hypoglycemia if a tumor is missed in these patients with negative preoperative imaging, however, the potential benefits of PVS is substantial. We have convincingly demonstrated that PVS is the single best preoperative localizing study and that intraoperative ultrasound (IOUS) is the single best intraoperative localizing maneuver. From a patient's perspective, if one had a rare, potentially life-threatening disease that had limited medical options for treatment, what would one want? From the viewpoint of cost-effectiveness, would it be correct to withhold a study that provides useful localizing information in at least three of four patients? The most cost-ineffective result would be unsuccessful surgery with persistent hypoglycemia. We have successfully avoided that problem in all but one of 12 patients with the methods described. Because of the rare nature of the problem and the remarkable success of our study (92%) in this subset of insulinoma patients with negative preoperative arteriographic studies, one can only do the same or worse by eliminating either PVS or IOUS, and not better.

J. A. NORTON, M.D.
T. H. SHAWKER, M.D.
J. L. DOPPMAN, M.D.
D. L. MILLER, M.D.
D. L. FRAKER, M.D.
D. T. CROMACK, M.D.
P. GORDEN, M.D.
R. T. JENSEN, M.D.
Bethesda, Maryland

March 8, 1991

Dear Editor:

The article "Mastectomy Following Preoperative Chemotherapy" by Broadwater et al., published in the February issue of *Annals of Surgery,* contains misleading conclusions based on inappropriate comparisons between small and widely disparate groups of surgical patients. The preoperative chemotherapy group received less extensive surgery (12% modified radical mastectomy) compared with the mastectomy-alone group (61% modified radical mastectomy). Details of postoperative chemotherapy and radiotherapy are omitted.

The authors observe that there is no statistically significant difference between groups with respect to wound infection, necrosis, or delay in institution of postoperative chemotherapy, but fail to acknowledge that the *trends* observed are contrary to their null hypothesis (and could, conceivably, achieve statistical significance given a larger sample size). Stratification to determine differences in complication rates between *appropriate* groups by controlling such parameters as tumor size, local grave signs, or extent of surgery is not done. The "statistically significant" decrease in seroma rate observed in the preoperative chemotherapy group is not surprising because only 12% of that group received a full axillary dissection (*versus* 61% in the mastectomy-alone group). Although there was no significant difference between groups in the number of lymph nodes in the operative specimens, the numbers of nodes obtained are quite small (and documentation of how the nodal statistics are derived is not provided). The seroma rate of 28% in the mastectomy-alone group seems unusually high when compared with other modern surgical series.

The authors observe a significant decrease in overall survival among neoadjuvant patients when chemotherapy was delayed more than 30 days, but are unable to stratify this by stage or performance status. Similar analysis of the mastectomy-alone group is not provided. Although "significance" was not achieved between the 30% of neoadjuvant patients and the 20% of the "control" patients whose postoperative systemic therapy was delayed, there is an absolute difference that might become significant with larger sample size. If delaying postoperative chemotherapy truly imparts a negative survival advantage, preoperative chemotherapy could conceivably be *detrimental* to survival.

The authors summarize that patient survival has improved with the use of preoperative therapy, but such a claim has been substantiated by neither their own study nor by randomized prospective trials comparing preoperative with standard postoperative chemotherapy. The case for neoadjuvant chemotherapy has been largely based on inappropriate comparisons between outdated historical control groups who received no chemotherapy and highly selected, favorable subgroups from nonrandomized neoadjuvant trials. At the Medical College of Virginia, a group of 118 patients with stage III breast cancer (1983 AJCC criteria, including 13 patients with stage IIIB inflammatory disease) treated with primary surgery and standard postoperative chemotherapy for positive nodes demonstrated a median survival of 69 months.[1] By comparison, the median survival of 54.3 months cited by the authors does not constitute an improvement in patient survival. Similarly modern prospective series using postoperative chemotherapy for locally advanced breast cancer document overall survival rates comparable to those touted by advocates of neoadjuvant therapy.[2,3]

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JAMES L. FRANK, M.D.
Springfield, Massachusetts

June 25, 1991

Dear Editor:

The purpose of our study was to examine the morbidity of aggressive preoperative chemotherapy in patients with advanced breast cancer to (1) determine if preoperative chemotherapy was safe, and (2) evaluate if our criteria for the timing of surgery were appropriate. This paper was not designed to analyze the efficacy of preoperative chemotherapy in the management of patients with stage III breast cancer.

There seems to be much confusion regarding the nomenclature for mastectomy. Extended simple mastectomy (ESM) is a mastectomy including a level I and level II axillary lymph node dissection. Modified radical mastectomy (MRM) is the same operation with the addition of removal of the level III lymph nodes. In this study and a previous analysis that we performed, these two operations are essentially equivalent with respect to morbidity and postoperative complication rates.[1] All patients with advanced primary breast cancer had the same postoperative chemotherapy and radiotherapy.

We agree with Dr. Frank that the sample size in our study is small and that a beta error effect could exist. This study, however, remains the only attempt in a large patient population with preoperative chemotherapy and mastectomy to define operative risk and evaluate criteria for timing of surgery. No significant increase in morbidity rate was documented by this study. We are confused by Dr. Frank's comments that seroma rates of 28% are unusually high; most studies document comparable (10% to 35%) seroma rates.[2]

Although we did not try to make a case for preoperative chemotherapy improving patient survival, we were interested in determining if surgical complications that delayed the reinstitution of systemic therapy might impact survival. A delay in instituting postoperative therapy in advanced primary breast cancer has previously been shown by us to impact survival, and this study only confirms and supports the previous report.[3] Dr. Frank is correct in stating that preoperative chemotherapy has not been shown to improve survival when compared with postoperative chemotherapy. Certainly, he would agree that all patients with advanced primary breast cancer should have aggressive systemic therapy. In addition, preoperative chemotherapy minimizes the extent of surgery required for effective local disease control. In our series, all patients had mastectomy without the need for chest wall resection, or skin grafting. It is not appropriate for him to compare survival in his series with our group of patients, because this analysis is meaningless.

We continue to support the use of preoperative chemotherapy in patients with advanced primary breast cancer. The high response rates allow surgical resection without the need for skin grafting or chest wall resection. Our study supports the safety of preoperative chemotherapy, and our criteria for the timing of surgery after aggressive chemotherapy seem appropriate. This information remains important because several cooperative groups are now using preoperative chemotherapy in clinical trials for less advanced breast cancers.

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J. Ralph Broadwater, M.D.
Michael J. Edwards, M.D.
Gabriel N. Hortobagyi, M.D.
Fred C. Ames, M.D.
Charles M. Balch, M.D.
Little Rock, Arkansas,
Louisville, Kentucky, and
Houston, Texas

June 19, 1991

Dear Editor:

The article by M. C. Wilhelm et al. (Nonpalpable Invasive Breast Cancer, 1991; 213:600–603) contains data for which there are alternate interpretations. First, the false-positive rate was 72%, meaning that almost three fourths of all biopsies were nonbeneficial. Second, the data are not population based and it is not known how many interval surfacing cancers occurred between screens. Third, the types of breast cancers detected by screening are more biologically indolent and have an anticipated longer survival as a result of the length bias sampling inherent in the screening method as well as a lead time bias. Fourth, in the absence of a population based study with controls, the statement cannot be made that the probability of dying of breast cancer has been reduced.

The fourth proposition has been reviewed by Eddy (Screening for Breast Cancer, *Ann Intern Med* 1989; 111:389–399). Eddy, analyzing all population-based controlled clinical trials, concluded that no more than an average of 25 woman-days of life can be anticipated from mammographic screening. For every 10,000 women screened for 10 years, there will be some 2500 false-positive diagnoses with biopsy. The cost for the general population will be about 1.3 billion dollars per annum.

The purpose of my comments is to raise caution in the interpretation of non–population-based, uncontrolled retrospective studies. They do not prove that the breast cancer problem is solved, and to imply that it is in such studies creates false expectations leading to a myriad of additional medical, medicolegal, and fiscal problems.

John S. Spratt, M.D.
Louisville, Kentucky

July 19, 1991

Dear Editor:

We appreciate the opportunity of replying to Dr. Spratt's letter. We agree that retrospective institutional reviews require cautious interpretation. This paper sheds light on the prognosis of, and by extension, treatment requirements for women with invasive cancer detected by screening mammography. We do not think, however, that the breast cancer problem is solved.

The false-positive rate of mammography was 83% at our institution. This is similar to other large series, as outlined in the paper and discussion session. We believe that this is a major issue in breast cancer today. The high number of negative biopsies performed in the United States strains resources, is psychologically devastating to women, and may keep women from screening. Research with techniques such as stereotaxic localized sampling is necessary to reduce the need for surgical biopsy. This issue is irrelevant to the subject of the paper, however.

Similarly, Dr. Spratt's second and last points on the role of screening are important, but of little bearing on the issues we raise in the paper. Although Eddy argues that breast cancer screening is at best minimally cost effective, there are ample controlled population based data that screening reduces breast cancer mortality.

The last point is that screening-detected cancers are more indolent. As reviewed in our paper, we and others found metastatic nodal disease in screening-detected cancer with alarming frequency (about 20%). These women fare as poorly as women with larger tumors with involved nodes. For those without nodal metastases, this and other series, some with much longer follow-up, show that these women do exceptionally well. Indeed, they do much better than T1 N0 groups in controlled adjuvant trials. This suggests that women with screening-detected, node-negative, invasive breast cancer are a subset for whom the adjuvant therapy beneficial for node-negative women in general is not necessary.

Morton C. Wilhelm, M.D.
Stephen B. Edge, M.D.
Diane Cole, B.A.
Ellen S. deParades, M.D.
Henry Frierson, M.D.
Charlottesville, Virginia

September 26, 1990

Dear Editor:

We were very much pleased by the paper "Survival Following Locoregional Recurrence After Breast Conservation Therapy for Cancer" by Stotter et al., vol. 212, no. 2, pp 166–172. It is certainly difficult to believe that a local recurrence after breast-conserving treatment (BCT) for breast cancer would not bear the inherent risk of metastases and subsequent death, just like a second primary. Until now, only one empirical study has confirmed the hypothesis that, in the long run, survival after local recurrence would be impaired.[1]

We want to make some remarks with regard to the methods applied.

(1) No distinction was made between local (confined to the breast), locoregional (in both breast and lymph nodes), and regional (localized only in the lymph nodes) recurrences. This is certainly not appropriate, because the essential difference between mastectomy and BCT is the possibility of recurrence in the preserved breast. Regional recurrences are not more frequent after breast-conserving treatment than after mastectomy. The treatment of the axilla is the same in both treatment modalities. It would have been more appropriate to perform this procedure for local and locoregional recurrences only. Now the relative survival deficit after BCT due to locoregional recurrence in comparison with mastectomy is probably overestimated.

(2) The validity of the exponential model applied (also known as the DEALE) is not shown. This model, using a decreasing exponential function for survival, assumes that the hazard rate is constant.[2,3] This is probably not the case in breast cancer, especially not in the first 5 to 10 years after diagnosis.[4] Furthermore, Beck et al. showed that a decreasing exponential survival function to estimate the life expectancy (which is the inverse of the hazard rate) only was valid in diseases with hazard rates exceeding 0.1 per year; otherwise mortality will be overestimated.[2] It is possible to compute the yearly mortality forces or hazard rates from the monthly values mentioned in the paper of Stotter et al. simply by multiplying them by a factor of 12. The yearly hazard rates, recalculated in this way, equal approximately 0.01 per year for stage 0 patients, 0.032 per year for stage I patients, 0.05 per year for stage II patients, and 0.11 per year for stage III patients. Thus, the real survival deficit due to local recurrences will be somewhat lower than suggested in the paper.

(3) The really important point is not whether the survival deficit exists, but whether it is clinically important, if it exists. This might be explored by a clinical decision analysis, in which mathematical models can be applied to model the possible survival deficit, but also other factors, such as age of the patient and quality of survival, can be integrated to come to a balanced judgment about the potential impact of the local recurrence risk on the lives of breast cancer patients.

References

1. Clark RM. Alternatives to mastectomy—The Princess Margaret Hospital experience. *In* Harris JR, Hellman S, Silen W, eds. Conservative Management of Breast Cancer. Philadelphia: JB Lippincott, 1983, pp 35–46.
2. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the 'DEALE'): I. Validation of the method. Am J Med 1982; 73:883–888.
3. Stalpers LJA, Gasteren van HJM, Daal van WAJ. DEALE-ing with life-expectancy and mortality rates. Med Decis Making 1989; 9: 150–152.
4. Pierquin B, Marin L. The past and future of conservative treatment of breast cancer. Am J Clin Oncol 1986; 9:476–480.

LIA C. G. VERHOEF, M.D.
LUKAS J. A. STALPERS, M.D.
PROF. WILLEM A. J. VAN DAAL, M.D.
Nijmegen, The Netherlands

October 29, 1990

Dear Editor:

We would like to thank Drs. Verhoef and Stalpers and Prof. van Daal for their interest in our paper.

Taking their points in sequence:

(1) In the part of our paper in which we compared the outcome in those of a cohort of patients with locoregional recurrence with the rest, we were able to take into account the site (breast and/or axilla) and extent of recurrence because we had that detailed information about our patients' recurrences. Thus, in our mathematical model, we apportioned a hazard for locoregional recurrence according to its "stage." A smaller hazard was apportioned for a small breast recurrence not involving skin, and a larger hazard as tumor size increased, if poor-prognosis local features were present, and particularly if lymph nodes were involved (even if no breast recurrence was evident). When assessing the results of published trials, such detail was not possible because the precise location and extent of locoregional recurrences have not been included in the publications.

(2) Gore et al. showed that hazard rates for treated breast cancer patients are higher for higher-stage disease, increase during the first 1 to 4 years, and then decline and converge on a constant level. The initial rise was negligible for small tumors, however, the hazard rate being essentially constant with time, indicating that the exponential curve is a good approximation in early-stage disease. The exponential model was chosen mainly for its simplicity, however. Our calculations then could be simple and, although the choice of curve influences the details of the predictions, it does not alter the overall pattern. We hoped thereby that our potential audience would not be put off: we wanted to obtain the attention of a wide range of clinicians, including those unfamiliar with such use of mathematical formulae and detailed statistical analysis. Our purpose was to reopen the issue of local recurrence and its possible impact on survival. Choosing the most accurate mathematical form to model the survival curve was considered less important than getting the overall message across.

If the choice of the exponential curve has led to an overestimate of the hazard related to locoregional recurrence, our ignoring second and subsequent recurrences will have led to underestimation. The two may well balance out.

(3) We agree with the final points. We did not intend our paper to indicate that breast conservation treatment for early breast cancer should be eschewed. We are suggesting a small risk affecting a minority of patients. It will regularly be outweighed in the older patient, the unfit, and particularly in the woman keen to preserve her breast.

Reference

Gore SM, Pocock SJ, Kerr JR, et al. Regression models and non-proportional hazards in the analysis of breast cancer survival. Appl Statist 1984; 33:176–195.

ANNE STOTTER, PH.D., F.R.C.S.
Leicester, England

November 27, 1990

Dear Editor:

Stotter et al. studied the survival risk of local recurrence after preservation surgery.[1] Most of the patients returned with recurrences that were larger than their primary lesions. Was the survival hazard of local recurrence confined to this group of patients? Over the past 10 years, I have suggested that patients who survive their first breast cancer without developing distant disease can be expected to survive a similar volume of tumor in adjacent breast or lymphatic tissue.[2,3] Stotter's data are consistent with this thesis.

The authors cite the second Guy's Hospital trial in which patients with stage I disease benefitted from mastectomy. The survival benefit was actually confined to patients with T1 lesions.[4] The surgical practice at M. D. Anderson Hospital is the opposite of that concluded by this trial. The authors did not explain this paradox, for which I have previously offered an explanation.[5] Do Balch and his co-authors find any fault with my explanation?

They concluded that 10,000 patients would have to be monitored for more than 10 years to detect the survival hazard of locoregional recurrence. Because no consistent survival advantage has been shown for adjuvant radiation, patients should be informed that the survival benefit of radiation is negligible or very small indeed.

References

1. Stotter A, Atkinson EN, Fairston A, et al. Survival following locoregional recurrence after breast conservation therapy for cancer. Ann Surg 1990; 212:166–172.
2. Evans R. Host resistance to carcinoma of the breast. South Med J 1980; 73:1261–1263.
3. Evans R. The "seed and soil" hypothesis and the decline radical surgery: a surgeon's opinion. Tex Med 1990; 86:85–89.
4. Hayward J, Caleffi M. The significance of local control in the primary treatment of breast cancer: Lucy James Wortham Clinical Research Award. Arch Surg 1987; 122:1244–1247.
5. Evans R. Natural killer cells and the Guy's Hospital trials [letter]. Arch Surg 1988; 123:914–915.

RICHARD A. EVANS, M.D.
Houston, Texas

January 12, 1991

Dear Editor:

One of the most important points we wished to make in our paper was that it was not possible to prove, or disprove, a survival hazard due to local recurrence. This is partly because local recurrence is not a frequent event; partly because the likely effect, if any, is relatively small; and partly because of insufficient numbers of patients in the relevant randomized trials, followed for insufficient time. There is therefore no question, at present, of identifying a subgroup of those patients developing local recurrence to which a survival hazard is confined.

We predict that patients with small recurrences have a higher chance of survival than those with large recurrences, just as those with small primaries are known to do better than those with large primaries. Dr. Evans has proposed the mechanism for this being that each patient can tolerate a certain tumor burden (perhaps related to natural killer cell activity), constant over the years, and clinical metastasis only develops when that threshold is exceeded. In our model, we postulated that the chance of tumor emboli surviving and growing increased continuously with increasing tumor burden, with no critical cutoff. Both theories imply that local tumor is a source of metastatic disease, and that the less there is of it over the years, the greater the chance of patient survival.

The results of the second Guy's Hospital trial can be interpreted as indicating that more radical surgery resulted in improved survival for those women with stage I as compared with stage II disease. This was not shown in the first Guy's trial, however, and has not been supported by other randomized controlled trials of mastectomy compared with breast conservation therapy. The M. D. Anderson, like every other major center worldwide, considers breast conservation therapy as an alternative to mastectomy predominantly for women with early stage disease.

Considerable data support the statement that adjuvant radiotherapy conveys no survival benefit after mastectomy. We cannot necessarily extrapolate from this to the situation where the breast has been preserved. We know that in breast conservation therapy there is a tradeoff between surgery and radiotherapy in achieving local control, whereby higher radiation doses can compensate for closer surgical margins. Dr. Evans has himself emphasized that local recurrence after mastectomy behaves like metastatic disease, whereas local recurrence after breast conservation therapy is different. He has proposed that the latter be termed "local persistence" to emphasize the fact that it behaves more like primary tumor. The results of the NSABP B-06 trial show that if we use breast-conserving surgery without adjuvant radiotherapy, we can expect a much higher local recurrence rate, itself unacceptable, regardless of the survival risks. The fact that patients in this arm of the trial have not fared significantly worse to date is to be expected from the numbers in the trial, the duration of follow-up, and the likely size of any resultant survival deficit. As we indicated in our paper, the likely survival deficit is small when considered in relation to the patient population as a whole, most of whom will not develop local recurrence. For the individual who does, we predicted approximately a doubling of her risk of dying of the disease.

ANNE STOTTER, PH.D., F.R.C.S.
Leicester, England

February 19, 1991

Dear Editor:

I read with interest the article by Peters et al., "Safety and Efficacy of Laparoscopic Cholecystectomy." Having performed over 100 laparoscopic cholecystectomies, I was pleased to finally see information reaching the journals regarding this procedure. I cannot help but to point out an absurdity in the article.

Under unresolved issues, the authors state "can this procedure be performed safely by the average general surgeon in the community and/or rural hospital?" The authors should be reminded that this procedure was developed by the average general surgeon in a community hospital. Furthermore, in the south, this procedure has been performed in almost every hospital for approximately 6 months.

I agree that there are many unresolved issues. However, most general surgeons that wish to take the time to learn this procedure and have appropriate equipment will be capable of safely performing laparoscopic cholecystectomies. The surgeons who are just beginning to gain experience with laparoscopic cholecystectomy should not think that this procedure needs to be limited to a few surgeons.

I believe the emphasis should be based on properly training any general surgeon who wishes to learn this procedure. Perhaps a demonstration of competence in this procedure by limited preceptorship would be wise. The current emphasis by certain surgeons to apparently accrue large sums of money by charging inordinate fees for preceptorship should be discouraged. If one has experience with laparoscopic cholecystectomy, he should share this experience with the fledgling laparoscopic surgeon for free (or at the very most, have his incurred expenses covered).

JOSEPH F. UDDO, JR., M.D.
Metairie, Louisiana

April 22, 1991

Dear Editor:

We would like to thank Dr. Uddo for his kind comments regarding the paper "Safety and Efficacy of Laparoscopic Cholecystectomy." We think he has pointed out some very accurate issues with regard to training and credentialling of surgeons in this area and we wholeheartedly agree with much that he says. We might remind him that the manuscript was prepared very early in the history of laparoscopic cholecystectomy. As he points out, and as has become clear over the ensuing months, this is a procedure that can be performed safely by the average general surgeon and, thus, we agree with his assessment.

Nevertheless, we might also add that we are becoming more convinced that it is a more dangerous procedure, however, than open cholecystectomy. We think the procedure is generally safe, given appropriate training, caution, and an accepting attitude toward conversion to open cholecystectomy, but it may represent an inherently increased risk over open cholecystectomy. Time will allow us the answer.

The issue of whether this procedure was actually devised by "average" general surgeons is certainly open to debate. As he knows, it originated in French clinics, and Dr. Mouret, who pioneered the procedure in France, is a clinical laparoscopist with extensive experience. Describing his laparoscopic abilities as average would be inadequate to say the least. In addition, although it was indeed developed at many community hospitals within the United States, we would also question whether the surgeons involved in such innovative endeavors could be described as average. We have had the opportunity to participate in training courses for laparoscopic cholecystectomy involving several hundreds of surgeons, and it has been our observation that there are many that find it difficult. It is by no means a natural extension of our usual surgical abilities.

Dr. Uddo seems offended by the assertion that we should question whether the average general surgeon is capable of performing new procedures. He also suggests that implied in our statement is an argument for limiting the procedure to a limited group of surgeons. The authors clearly did not intend any such meaning by posing the question. We think it would be inappropriate for us not to question whether any new procedure, especially one that is as technologically different as laparoscopic cholecystectomy, can be taken from the laboratory into the clinical realm with training that would be available and reasonable to the majority of surgeons and then could be applied safely. Thus, the intent of the question was exactly the opposite of Dr. Uddo's suggestions. We believe it would be highly inadequate to develop procedures that could not be easily expanded to the realm of the majority of surgeons quickly.

We agree with his assessment that the emphasis should be placed on proper training, including a demonstration of competence. The entrepreneurism that has been associated with this procedure is an unfortunate consequence of the realities of the 1990s marketplace and should be discouraged.

JEFFREY H. PETERS, M.D.
Columbus, Ohio

April 29, 1991

Dear Editor:

Dr. Simons' excellent letter describes the treatment of a young girl who presented with extrusion of a free fragment or "remnants" of spleen through a shrapnel wound in the left flank. Extrusion of a free fragment of liver or spleen devoid of blood supply is not unique, especially in patients with large wounds and significant intraperitoneal injury that leads to an elevated intraperitoneal pressure. The extrication of such exteriorized fragments from clothing, dressing, the cart, or from the wound edge bears no resemblance to the historical external splenectomies described by our forbears who identified ligation and division of the externalized splenic blood supply.

The word laparotomy is derived from the Greek word "lapara," which means loin or flank. Had Dr. Simons explored this patient through her flank wound, this "laparotomy" approach would have permitted safe vascular division with extrication of the fragmented spleen *and* repair of the injured diaphragm. Indeed, extension of a flank wound into a formal "laparotomy" is my preferred approach in a few carefully selected patients with a close-range shotgun blast that is clearly confined to the flank area. The decision by Dr. Simons to obtain intraperitoneal vascular pedicle control though the traditional anterior celiotomy permitted a more thorough inspection of the pancreas, which was normal. The fine result achieved by Dr. Simons reflects his decision to perform the traditional open approach by one of the many different anatomic pathways to achieve complete safe splenectomy. Dr. Simons' description of this girl's presentation, her interoperative findings, and the subsequent photograph of her flank wound on postoperative day 4 reinforce my conclusion that the beginning of the modern era of splenic surgery for trauma should be the splenectomy performed by Riegner, who, in 1893, performed an anterior celiotomy to remove the fractured spleen of a young man who had fallen from a scaffold.[1] John Hunter, the renowned 18th century anatomist and surgeon, would have recognized the distinct differences from the presentation of Dr. Simons' patient and the formal flank exposures by myself as compared with the historical splenectomies with extraperitoneal division of the vascular pedicle reported by his predecessors. John Hunter also would have recognized that deviation from the traditional historical concept invites excited commentary.

Reference

1. Riegner O. Ueber einen Fall Von Exstirpation der Traumatisch Zerrissenen Milz. Berl Klin Wochnschr 1893; 30:177–181.

CHARLES E. LUCAS, M.D.
Detroit, Michigan

March 7, 1991

Dear Editor:

It was with great interest that I read Dr. Lucas's article "Splenic Trauma, Choice of Management" (*Ann Surg* 1991; 213:98–112). His dismissal of the historical accounts of splenectomy, performed by detaching the spleen as it presented in the wound, is made on the basis of a lack of documented contemporary descriptions of spleens prolapsing from wounds. His conclusions, however, may be somewhat premature.

One of the first patients I saw as a Red Cross surgeon in Thailand was a 12-year-old girl who presented with a through-and-through shrapnel injury of the left flank in whom the remnants of her injured spleen were seen to be prolapsing from her wound.

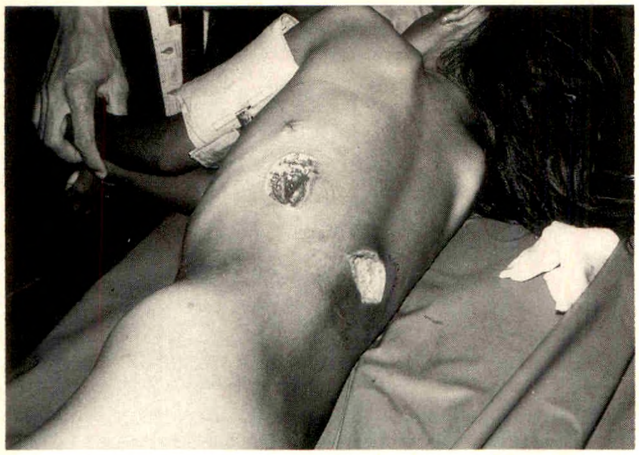

FIG. 1. Twelve-year-old Cambodian girl with a through-and-through shrapnel injury to her left flank, through which her injured spleen was protruding.

She was managed in the now traditional approach of exploratory laparotomy with completion splenectomy but, had we been so inclined, we could have accomplished amputation of the injured organ, where it presented in the primary wound. Laparotomy findings included a diaphragmatic tear and a severely damaged spleen that was separated from all its peritoneal attachments and freely mobile on its intact hilar pedicle. The pancreas was uninjured. The accompanying photograph (Fig. 1) was taken at the time of delayed primary wound closure, some 4 days after her laparotomy, and illustrates her through-and-through injury. The spleen was history by this time as, I suspect, may have been the case with her 17th and 18th century counterparts.

Medical progress requires constant critical evaluation of accepted tenets. To fully justify discounting historical descriptions, however, requires more than a want of similar personal experiences. After all, the 18th century saw some of the keenest observers in the history of surgery. John Hunter's name comes to mind.

RICHARD SIMONS, M.B.
Seattle, Washington

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David C. Sabiston, Jr., M.D.
Annals of Surgery
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Duke University Medical Center
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Type manuscript double spaced, including title page, abstract, text, acknowledgments, references, tables, and legends.

Each manuscript component should begin on a new page, in this sequence:

Title page
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Acknowledgments
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Submit the required number of copies of manuscript and figures (*see* journal's instructions) in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, as described in Submission of Manuscripts, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

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Type manuscript on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in. or 8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in.). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations. Begin each of the following sections on separate pages: title page, mini abstract, abstract, text, acknowledgments, references, individual tables, and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

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The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (counting letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

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A short description of the study should be submitted to appear on the table of contents. It should consist of approximately three sentences of no more than 50 words.

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The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Use only approved abbreviations (*see* list of Commonly Used Approved Abbreviations elsewhere in this document).

TEXT

The text of observational and experimental articles is usually, but not necessarily, divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Other types of articles such as case reports, reviews, and editorials may need other formats, and authors should consult individual journals for further guidance.

Introduction: Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

Methods: Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like sometimes may be suitably presented in the form of one or more appendixes.

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ACKNOWLEDGMENTS

Acknowledge only persons who have made substantive contributions to the study. Authors are responsible for obtaining written permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions.

REFERENCES

Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parenthesis). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus.* Use the style of the examples cited at the end of this section, which has been approved by the National Library of Medicine.

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The references must be verified by the author(s) against the original documents.

Examples of correct forms of references are given below.

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1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al.)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976; 294:687–690.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gammaglutamyltransferase in blood. Scand J Clin Lab Invest 1976; 36:119–125.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976; 5:224–225.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–471.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

Other Articles

8. Newspaper Article

   Shaffer RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. Wall Street Journal 1977 Aug 12:1(col. 1), 10(col. 1).

9. Magazine Article

   Roueché B. Annals of medicine: the Santa Claus culture. The New Yorker 1971 Sep 4:66–81.

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Type each table on a separate sheet: remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, **, ††. . . . Identify statistical measures of variations such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

Having too many tables in relation to the length of the text may produce difficulties in the layout of pages. Examine past issues of *Annals of Surgery* to estimate how many tables to use per 1000 words of text.

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Use only standard abbreviations (*see* below for lists of commonly used approved abbreviations). Consult the following sources for additional standard abbreviations: [1] Iverson, Cheryl et al., eds. American Medical Association manual of style, 8th ed. Baltimore: Williams & Wilkins, 1989. [2] CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington: Council of Biology Editors, 1978; and [3] O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam, Oxford, New York: Elsevier-Excerpta Medica, 1975. Avoid abbreviations in the title. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

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Standard Units of Measurement

Term	Abbreviation or Symbol
ampere	A
ångström	Å
barn	b
candela	cd
coulomb	C
counts per minute	cpm
counts per second	cps
curie	Ci
degree Celsius	°C
disintegration per minute	dpm
disintegration per second	dps
electron Volt	eV
equivalent	Eq
farad	F
gauss	G
gram	g
henry	H
hertz	Hz
hour	h
international unit	IU
joule	J
kelvin	K
kilogram	kg
liter	L
meter, metre	m
minute	min
molar	mol/L
mole	mol
newton	N
normal (concentration)	N
ohm	Ω
osmol	osmol
pascal	Pa
revolutions per minute	rpm
second	s
square centimeter	cm^2
volt	V
watt	W
week	wk
year	yr

Combining Prefixes

tera-	(10^{12})	T
giga-	(10^{9})	G
mega-	(10^{6})	M
kilo-	(10^{3})	k
hecto-	(10^{2})	h
deca-	(10^{1})	da
deci-	(10^{-1})	d
centi-	(10^{-2})	c
milli-	(10^{-3})	m
micro-	(10^{-6})	μ
nano-	(10^{-9})	n
pico-	(10^{-12})	p
femto-	(10^{-15})	f
atto-	(10^{-18})	a

Statistical Terms

correlation coefficient	r
degrees of freedom	df
mean	$\bar{x}$
not significant	NS

number of observations	n
probability	p
standard deviation	SD
standard error of the mean	SEM
"Student's" t test	*t* test
variance ratio	F

Others

adenosinediphosphatase	ADPase
adenosine 5′-diphosphate (adenosine diphosphate)	ADP
adenosine 5′-monophosphate (adenosine monophosphate, adenylic acid)	AMP
adenosine triphosphatase	ATPase
adenosine 5′-triphosphate (adenosine triphosphate)	ATP
adrenocorticotropic hormone (adrenocorticotropin)	ACTH
bacille Calmette-Guérin	BCG
basal metabolic rate	BMR
body temperature, pressure, and saturated	BTPS
central nervous system	CNS
coenzyme A	coA
deoxyribonucleic acid (deoxyribonucleate)	DNA
dihydroxyphenethylamine	dopamine
electrocardiogram	ECG
electroencephalogram	EEG
enteric cytopathogenic human orphan (virus)	ECHO
ethyl	Et
ethylenediaminetetraacetate	EDTA
gas-liquid chromatography	GLC
guanosine 5′-monophosphate (guanosine monophosphate, guanylic acid)	GMP
hemoglobin	Hb
logarithm (to base 10; common logarithm)	log
logarithm, natural	ln
methyl	Me
Michaelis constant	K_m
negative logarithm of hydrogen ion activity	pH
partial pressure of CO_2	P_{CO_2}
partial pressure of O_2	P_{O_2}
per	/
percent	%
radiation (ionizing, absorbed dose)	rad
respiratory quotient	RQ
specific gravity	sp gr
standard atmosphere	atm
standard temperature and pressure	STP
ultraviolet	uv
volume	vol
volume ratio (volume per volume)	vol/vol
weight	wt
weight per volume	wt/vol
weight ratio (weight per weight)	wt/wt

ABBREVIATIONS OF NAMES OF FREQUENTLY CITED JOURNALS

Acta Medica Scandinavica	Acta Med Scand
American Family Physician	Am Fam Physician
American Heart Journal	Am Heart J
American Journal of Cardiology	Am J Cardiol
American Journal of Clinical Nutrition	Am J Clin Nutr
American Journal of Clinical Pathology	Am J Clin Pathol
American Journal of Digestive Diseases	Am J Dig Dis
American Journal of Diseases of Children	Am J Dis Child
American Journal of Human Genetics	Am J Hum Genet
American Journal of the Medical Sciences	Am J Med Sci
American Journal of Medicine	Am J Med
American Journal of Obstetrics and Gynecology	Am J Obstet Gynecol
American Journal of Ophthalmology	Am J Ophthalmol
American Journal of Pathology	Am J Pathol
American Journal of Physical Medicine	Am J Phys Med
American Journal of Physiology	Am J Physiol
American Journal of Psychiatry	Am J Psychiatry
American Journal of Public Health	Am J Public Health
American Journal of Roentgenology	AJR
American Journal of Surgery	Am J Surg
American Journal of Tropical Medicine and Hygiene	Am J Trop Med Hyg
American Review of Respiratory Disease	Am Rev Respir Dis
Anaesthesia	Anaesthesia
Anesthesiology	Anesthesiology
Annals of Allergy	Ann Allergy
Annals of Internal Medicine	Ann Intern Med
Annals of Otology, Rhinology and Laryngology	Ann Otol Rhinol Laryngol
Annals of Surgery	Ann Surg
Annals of Thoracic Surgery	Ann Thorac Surg
Archives of Dermatology	Arch Dermatol
Archives of Environmental Health	Arch Environ Health
Archives of General Psychiatry	Arch Gen Psychiatry
Archives of Internal Medicine	Arch Intern Med
Archives of Neurology	Arch Neurol
Archives of Ophthalmology	Arch Ophthalmol
Archives of Otolaryngology	Arch Otolaryngol
Archives of Pathology and Laboratory Medicine	Arch Pathol Lab Med
Archives of Physical Medicine and Rehabilitation	Arch Phys Med Rehabil
Archives of Surgery	Arch Surg
Arthritis and Rheumatism	Arthritis Rheum
Blood; Journal of Hematology	Blood
Brain; Journal of Neurology	Brain
British Heart Journal	Br Heart J
British Journal of Obstetrics and Gynaecology	Br J Obstet Gynaecol
British Journal of Radiology	Br J Radiol
British Journal of Surgery	Br J Surg
British Medical Journal	Br Med J
Canadian Journal of Public Health	Can J Public Health
Canadian Medical Association Journal	Can Med Assoc J
Cancer	Cancer
Chest	Chest
Circulation; Journal of the American Heart Association	Circulation
Circulation Research	Circ Res
Clinical Pediatrics	Clin Pediatr (Phila)
Clinical Pharmacology and Therapeutics	Clin Pharmacol Ther
Clinical Science and Molecular Medicine	Clin Sci Mol Med
Clinical Toxicology	Clin Toxicol
Diabetes	Diabetes
DM, Disease-a-Month	DM
Endocrinology	Endocrinology
Gastroenterology	Gastroenterology
Geriatrics	Geriatrics
Gut	Gut
Human Pathology	Hum Pathol
Investigative Radiology	Invest Radiol
JAMA; Journal of the American Medical Association	JAMA
Journal of Allergy and Clinical Immunology	J Allergy Clin Immunol
Journal of Applied Physiology	J Appl Physiol
Journal of Biological Chemistry	J Biol Chem
Journal of Bone and Joint Surgery; American Volume	J Bone Joint Surg [Am]
Journal of Bone and Joint Surgery; British Volume	J Bone Joint Surg [Br]
Journal of Clinical Endocrinology and Metabolism	J Clin Endocrinol Metab
Journal of Clinical Investigation	J Clin Invest
Journal of Clinical Pathology	J Clin Pathol
Journal of Experimental Medicine	J Exp Med
Journal of Gerontology	J Gerontol
Journal of Immunology	J Immunol
Journal of Infectious Diseases	J Infect Dis
Journal of Investigative Dermatology	J Invest Dermatol
Journal of Laboratory and Clinical Medicine	J Lab Clin Med
Journal of Laryngology and Otology	J Laryngol Otol
Journal of Medical Education	J Med Educ
Journal of Nervous and Mental Disease	J Nerv Ment Dis
Journal of Neurosurgery	J Neurosurg
Journal of Pathology	J Pathol
Journal of Pediatrics	J Pediatr
Journal of Physiology	J Physiol
Journal of Thoracic and Cardiovascular Surgery	J Thorac Cardiovasc Surg
Journal of Trauma	J Trauma
Journal of Urology	J Urol
Lancet	Lancet
Medical Clinics of North America	Med Clin North Am
Medical Letter on Drugs and Therapeutics	Med Lett Drugs Ther
Medicine (Baltimore)	Medicine (Baltimore)
New England Journal of Medicine	N Engl J Med
Obstetrics and Gynecology	Obstet Gynecol
Pediatrics Clinics of North America	Pediatr Clin North Am
Pediatrics	Pediatrics
Physiological Reviews	Physiol Rev
Plastic and Reconstructive Surgery	Plast Reconstr Surg
Postgraduate Medicine	Postgrad Med
Progress in Cardiovascular Diseases	Progr Cardiovasc Dis
Public Health Reports	Public Health Rep
Radiology	Radiology
Rheumatology and Rehabilitation	Rheumatol Rehabil
Seminars in Roentgenology	Semin Roentgenol
Surgery	Surgery
Surgery, Gynecology and Obstetrics	Surg Gynecol Obstet

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Bile Duct Injury During Laparoscopic Cholecystectomy

In the lead article in this month's issue, Davidoff and colleagues describe the patterns of injury of the extrahepatic biliary tree that occur during laparoscopic cholecystectomy. They show how mistaking the common bile duct for the cystic duct can lead to the most common kind of injury: resection of a segment of the common bile duct, often accompanied by injury to the right hepatic artery. The cause of this lesion is misinterpretation of the anatomy, where the common duct is thought to be the cystic duct. The second most common cause of ductal injury is hilar bleeding; as attempts are made to control bleeding, adjacent structures can be injured by the electrocautery, laser, or hemostatic clips.

The most critical issue raised by these cases concerns prevention. In an earlier article, Meyers and fellow members of the Southern Surgeons Club[1] reported that the rate of bile duct injury was 2.2% during a surgeon's first 13 laparoscopic cholecystectomies, but it dropped to 0.1% in subsequent cases. Data from the current study corroborate that finding; 10 of the 12 biliary injuries occurred during the surgeon's first dozen or so cases. These findings suggest that at present most biliary injuries are related to inexperience and are theoretically avoidable. They also suggest that the recommended privileging guidelines for laparoscopic cholecystectomy, which call for an experienced laparoscopic surgeon to serve as assistant during a surgeon's first three to six laparoscopic cholecystectomies, either have not been followed or are inadequate. The purpose of the proctoring recommendation is to minimize the risks of inexperience, and there is every reason to expect that it should prevent bile duct injuries. The observation in both studies that the steepest part of the learning curve comprises the first 12 cases could be interpreted to suggest that proctoring should now be increased to the surgeon's first 12 cases.

Hunter[2] recently proposed five technical steps aimed at preventing bile duct injuries during laparoscopic cholecystectomy: 1) promoting liberal use of the 30° angled laparoscope, because it provides a more perpendicular view of the hilar structures; 2) using firm cephalad retraction on the fundus of the gallbladder, which exposes the hilar structures; 3) having the first assistant retract the infundibulum of the gallbladder laterally instead of parallel to the common duct to separate of the cystic and common ducts; 4) dissecting the cystic duct continuously into the gallbladder; and 5) converting to an open cholecystectomy whenever bleeding becomes more than a minor problem. I would add the following items to that list: 6) using a cautery device with suction/irrigation capabilities because it allows the surgeon to keep the operative field much cleaner; 7) using caution when interpreting cholangiogram findings because it may be more difficult than anticipated to recognize when the cholangiogram catheter enters the common duct rather than the cystic duct; 8) always assuming that the common duct is occluded when it does not opacify; and 9) never using the cautery, laser, or clips blindly to control bleeding. In general, however, I believe that most duct injuries that occur during laparoscopic cholecystectomy can be avoided by more thorough proctoring of neophyte laparoscopic surgeons, more liberal (routine) use of cholangiography, and a greater willingness to convert to open cholecystectomy when the dissection becomes bloody or is otherwise difficult.

Laparoscopic cholecystectomy has only been performed widely in the US for about 2 years. In a sense, it is fortunate that specific information on bile duct injuries has become available so soon, because it provides clear directions for prevention. Davidoff and colleagues have performed a commendable service. It is now critical that those engaged in laparoscopic surgery use this information and do everything practical to minimize the frequency of this serious complication.

Reference

1. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991; 324:1073.
2. Hunter JG. Avoidance of bile duct injury during laparoscopic cholecystectomy. Am J Surg 1991; 161:71.

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San Francisco, California

WHAT'S NEW IN GENERAL SURGERY

Mechanisms of Major Biliary Injury During Laparoscopic Cholecystectomy

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Laparoscopic cholecystectomy has become the procedure of choice for surgical removal of the gallbladder. The most significant complication of this new technique is injury to the bile duct. Twelve cases of bile duct injury during laparoscopic cholecystectomy were reviewed. Eight injuries were of a classic type: misidentification of the common duct for the cystic duct, resection of part of the common and hepatic ducts, and associated right hepatic arterial injury. Another injury was similar: clip ligation of the distal common duct with proximal ligation and division of the cystic duct, resulting in biliary obstruction and leakage. Three complications arose from excessive use of cautery or laser in the region of the common duct, resulting in biliary strictures. Evaluation of persistent diffuse abdominal pain led to the recognition of ductal injury in most patients. Ultimately, 10 patients required a Roux-en-Y hepaticojejunostomy to provide adequate biliary drainage. One patient had a successful direct common duct repair, and the remaining patient underwent endoscopic dilatation.

ENTHUSIASM FOR LAPAROSCOPIC cholecystectomy has grown rapidly as recent reports have detailed the ease, efficacy, and safety of this procedure.[1-6] The Southern Surgeons Club reported an initial experience with 1518 cases collected during 1990,[7] and their experience has grown to over 9000 cases through early 1991. The overall complication rate reported in that series was small (5.1%) and included a number of very minor postoperative problems.

With the introduction of this new technique has come a learning period in which inexperience has resulted in a higher initial complication rate than will be expected later. The learning curve is highlighted in the Southern Surgeons Club experience by the incidence of bile duct injury. Within the first 13 cases of any participant's experience, the bile duct injury rate was 2.2%, compared with 0.1% after the 13th case.[7] The overall incidence of undetected common or hepatic duct injury was small (0.2%) in that series; however, those complications caused significant complications. This report documents and analyzes a series of 12 common or hepatic duct injuries that occurred during laparoscopic cholecystectomy and were subsequently referred to one medical center. This medical center had participated in the Southern Surgeons Club experience, but the injuries described here occurred outside of that experience. The videotapes of all but three original operations in which the injuries occurred were available, providing an opportunity to correlate intraoperative events with subsequent pathologic findings and to make suggestions for avoiding these complications.

Clinical Materials

The patients in this series were all referred to one surgeon at Duke University Medical Center for definitive care or advice in management of common or hepatic duct injuries sustained during laparoscopic cholecystectomy in the 11-month period from June 1990 through April 1991. The patients were referred by their primary physician within days of recognition of their injuries. As part of the management of these patients, operative videotapes were reviewed when available, in addition to the hospital records and roentgenograms. In each case, a precise mechanism seemed apparent, and subsequent operative findings, management, and clinical course correlated well with the presumed mechanism. The patients were seen regularly in follow-up after hospital discharge for 2 to 10

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months. Postoperative cholangiographic studies were performed only on the basis of clinical indications.

Results

Patient Profile

Twelve patients, seven women and five men, aged 22 to 76 years (mean, 45.4 years) were referred to Duke Medical Center. All but one patient had undergone laparoscopic cholecystectomy for chronically symptomatic gallstones demonstrated by ultrasound. The remaining patient had undergone laparoscopic cholecystectomy for acute cholecystitis confirmed radiographically by nonvisualizing oral cholecystogram (OCG) and endoscopic retrograde cholangiopancreatography (ERCP). Only one patient had another significant medical problem, that being severe coronary artery disease.

Original Procedure

The 12 patients in this series were referred by 11 general surgeons. Ten of these cases occurred within the first 11 laparoscopic procedures for these surgeons (1, 1, 3, 6, 7, 8, 9, 10, 11, and 11), whereas one case was the 91st of one surgeon's experience and another was the 100th. Nine surgeons performed the original procedure without other physicians assisting, and two were assisted by a second surgeon. Seven of the procedures were thought to have been "uncomplicated," whereas five were made difficult by significant inflammatory reaction around the gallbladder or portal area. Only three intraoperative cholangiograms were performed. Each was thought to have been normal; two patients subsequently developed common hepatic duct stricture, and the other was found to have partial ligation of the common duct. Five surgeons described significant intraoperative bleeding. One laparoscopic cholecystectomy was converted to an open laparotomy because of uncontrolled hemorrhage, and one patient was returned to the operating room for open exploration and right hepatic artery ligation after a significant hypotensive episode in the recovery room. In the remaining three cases, bleeding was adequately controlled laparoscopically.

Diagnosis of Biliary Injury

None of the ductal injuries reported in this survey were recognized at the time of the initial laparoscopic procedure. The diagnosis of a biliary injury was made 4 to 14 days after laparoscopic cholecystectomy in all but three of the patients; one was diagnosed on the first postoperative day, one was diagnosed 30 days after the initial procedure, and the other was diagnosed 6 weeks after the original procedure. In each case except one, evaluation of the patient's complaints of persistent diffuse pain eventually led to the discovery of bile duct injury. The remaining patient complained only of anorexia and fatigue 2 weeks after laparoscopic cholecystectomy. Laboratory studies disclosed an elevated total bilirubin in eight patients, with six being frankly jaundiced. The diagnosis of bile duct injury was established by ERCP in all but two patients. The diagnosis was made by percutaneous transhepatic cholangiography in one patient (Fig. 1A) after computerized tomography (CT) showed abnormal fluid collections, and by biliary scintigraphy in the other patient.

Initial Surgical Management

Four patients underwent surgical procedures subsequent to the diagnosis of biliary injury and before referral. Primary reanastomosis of transected bile ducts was attempted in two patients, but each failed because of anastomotic breakdown. A third patient simply had a tube placed into the proximal and distal ends of a divided ductal system for future identification of the anatomy, and the fourth simply had a subhepatic drainage catheter placed for collection of biliary ascites. The remaining patients were referred immediately to Duke on the recognition of biliary ductal injury.

Preoperative Management Following Transfer

Percutaneous transhepatic cholangiography or ERCP was performed at Duke after transfer in all cases to determine the precise site of injury. Cholangiography was followed immediately by CT scan to document or treat biliary leakage (four patients), as confirmed by demonstrating cholangiographic contrast material free in the peritoneal cavity (Fig. 2). One patient additionally had a perisplenic abscess drained by percutaneous techniques. All but one patient underwent preoperative placement of percutaneous transhepatic biliary catheters into the right and left hepatic ducts, both to determine the biliary anatomy and to assist in the identification of the proximal ductal system at laparotomy (Fig. 1B).

Description of Injuries

A definitive diagnosis was established by cholangiography in all cases. Eight patients had biliary obstruction due to partial (four) or complete (four) ligation of the biliary system (Fig. 3). Cholangiography demonstrated that four patients had completely decompressed ducts with subhepatic leakage of contrast and bile, but no ductal obstruction. The proximal borders of injury were as follows: common hepatic duct (five patients), confluence of the hepatic ducts (three patients), right hepatic duct (one patient), common duct (one patient), and several secondary hepatic biliary radicles (two patients). There were three strictures, two long and one short, with a continuous biliary system (Fig. 4). Each stricture was of the common

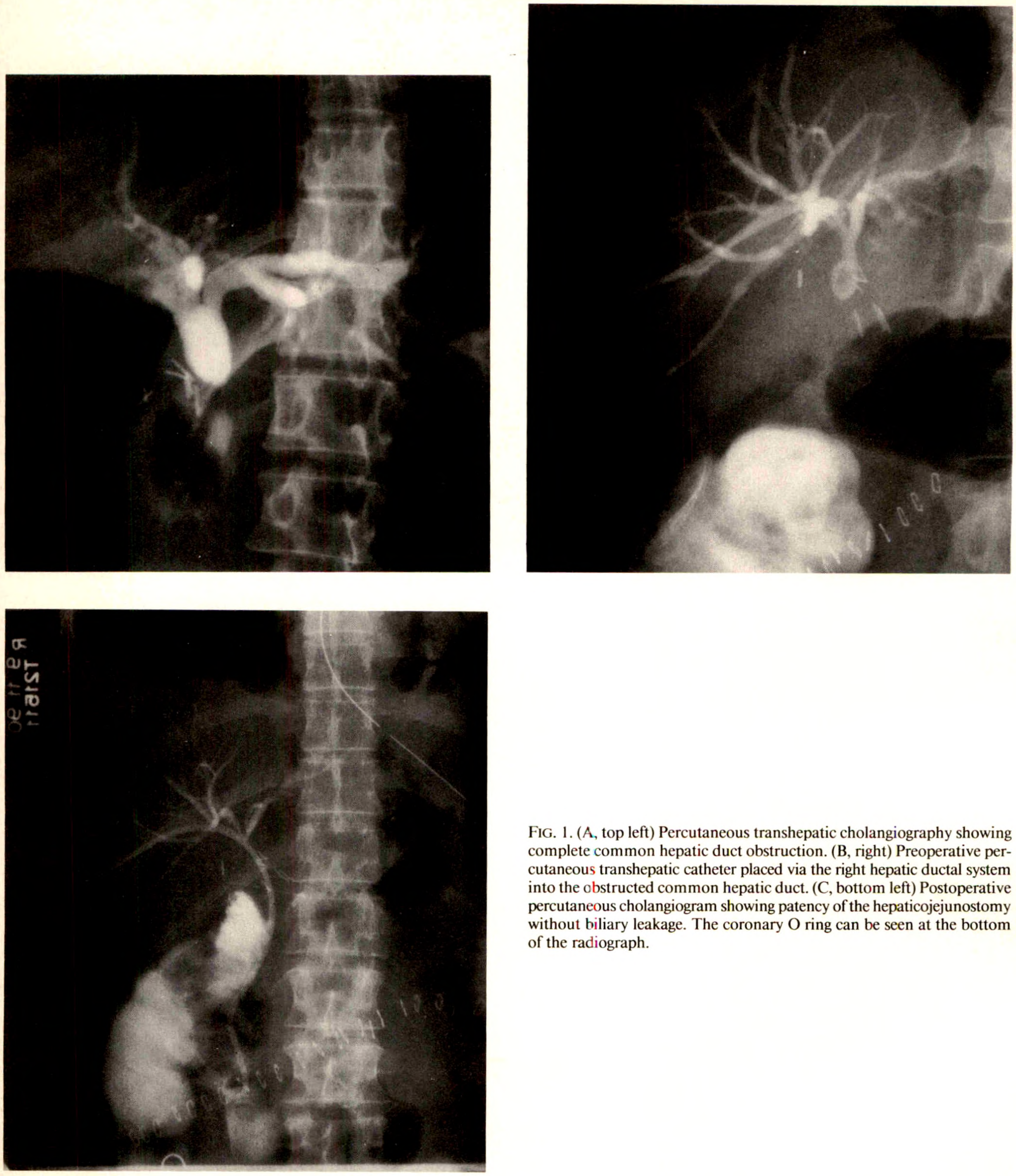


FIG. 1. (A, top left) Percutaneous transhepatic cholangiography showing complete common hepatic duct obstruction. (B, right) Preoperative percutaneous transhepatic catheter placed via the right hepatic ductal system into the obstructed common hepatic duct. (C, bottom left) Postoperative percutaneous cholangiogram showing patency of the hepaticojejunostomy without biliary leakage. The coronary O ring can be seen at the bottom of the radiograph.

hepatic duct system, with two extending into the common duct (*i.e.,* extending across the cystic duct junction). One patient had biliary leakage from an unligated cystic duct stump with complete common duct obstruction distally due to clip ligation (Fig. 5), suggesting that the distal "cystic duct" clips had been placed on the common duct. In each case without stricture in which cholangiography was performed, clips marked the distal ductal obstruction.

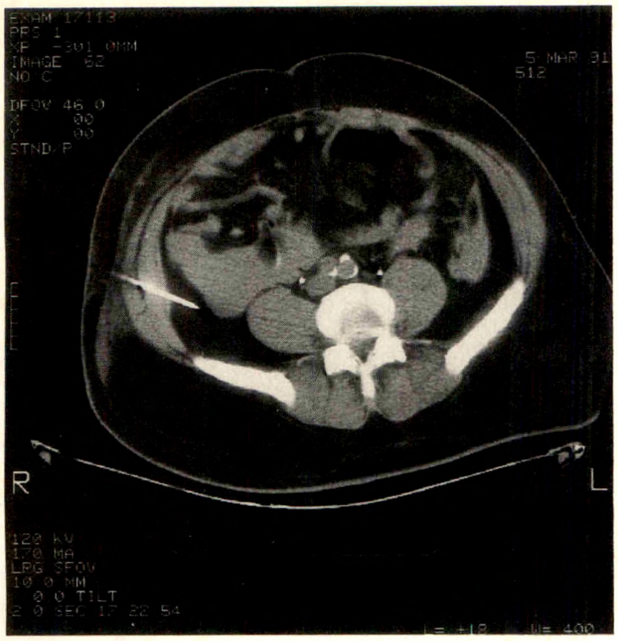


FIG. 2. Computed tomography–guided aspiration of intraperitoneal bile collection. This procedure was performed immediately after percutaneous transhepatic cholangiography. Note the presence of contrast material in the most dependent portion of this collection, confirming biliary leakage.

Review of Laparoscopic Videotapes

Each videotape was reviewed in its entirety after cholangiography and before surgery. In each case the injury was precisely identified, except in the three cases in which a stricture was presumed to have been secondary to repeated use of cautery or laser in the hilar area. In all but one of the other cases, inaccurate placement of the clips was seen with division of the bile duct and ligation or perforation of the right hepatic artery. Before division of the duct, in most cases, a small vascular branch to the common duct was clipped and divided as though it were the cystic artery (Fig. 3C).

Inadequate visualization of the operative field was obvious from the beginning of the film in four cases, indicating the surgeons' inexperience with laparoscopy. In no case was there camera or other equipment malfunction. In two cases the procedure was converted to open laparotomy because of significant bleeding. In one, brisk hemorrhage from the right hepatic artery obscured the scope and the procedure was immediately converted to an open one. In the other, the patient was initially observed in the recovery room but was returned to the operating room after a significant hypotensive episode. In

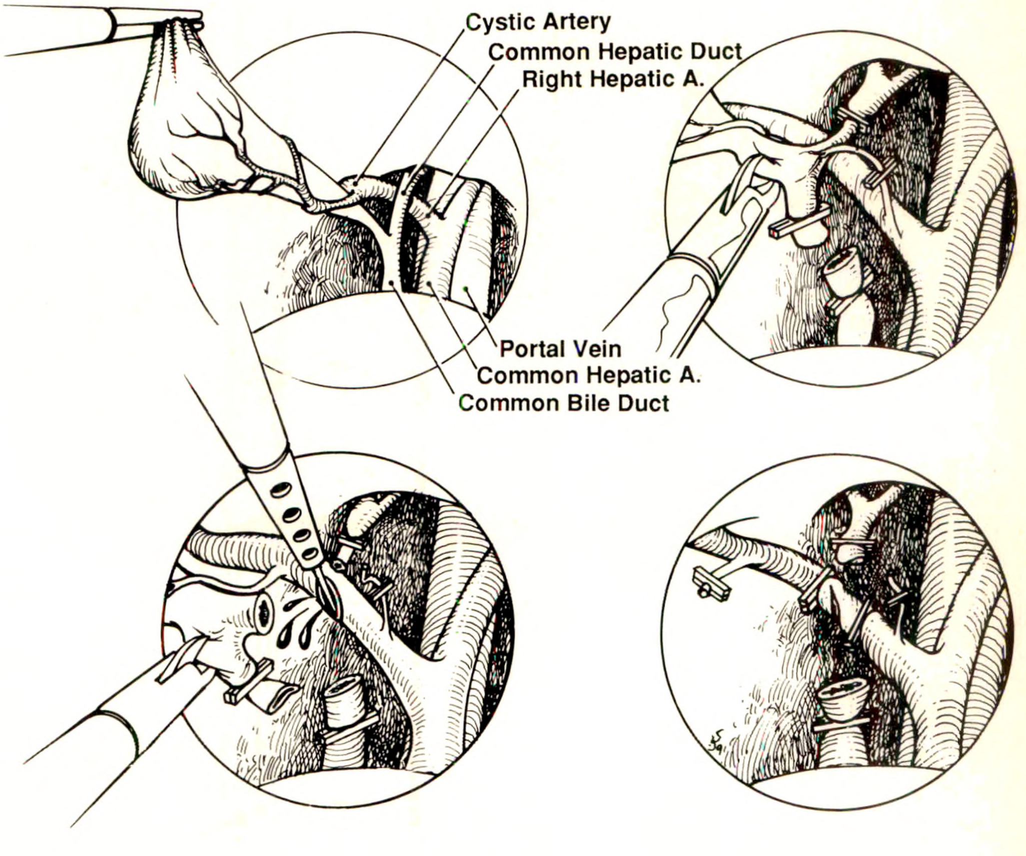
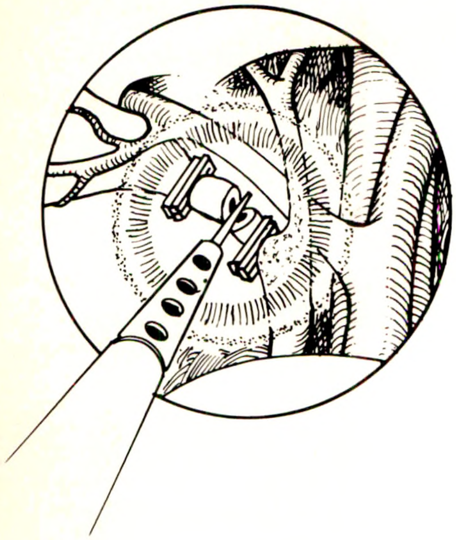


FIG. 3. The classic laparoscopic biliary injury. (A, top left) Normal portal anatomy. (B, top right) Misidentification of the common duct for the cystic duct, with subsequent ligation and division. (C, bottom left) Misidentification of the small arterial supply to the common duct for the cystic artery, with subsequent ligation and division. Note also injury of the right hepatic artery that invariably occurred during proximal division of the common hepatic duct. (D, bottom right) Ligation of the right hepatic artery and complete obstruction of the biliary system.



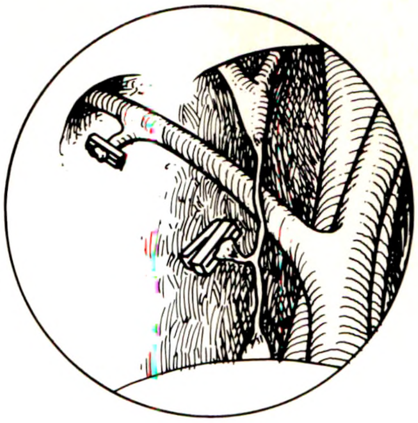


FIG. 4. Thermal injury to the portal triad, resulting in biliary stricture.

two cases obscured by significant scarring of the portal region, the grasping forceps were placed on the common duct rather than on the ampulla of the gallbladder during the dissection. The most common injury (Fig. 3) was dissection of the common hepatic and common bile ducts as though they were the cystic duct, division with or without clip ligation of the proximal hepatic ductal system, and then perforation or ligation of the right hepatic artery after initiation of cautery or laser dissection. In most cases significant bile leakage was present during much of the dissection. In all but two of the laceration injuries, there was excessive use of prograde rather than retrograde dissection of the presumed cystic duct, in other words, dissection primarily aimed toward the gallbladder rather than away from it.

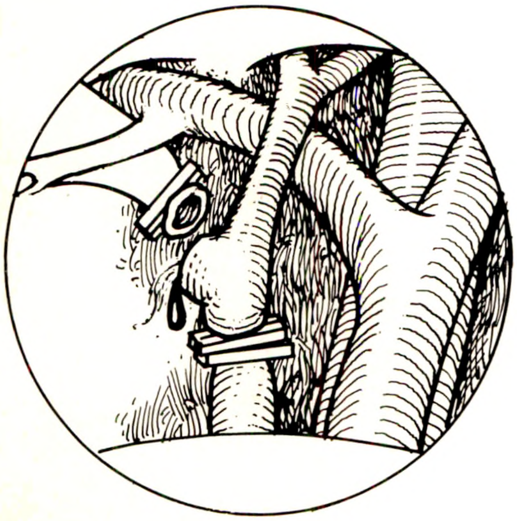


FIG. 5. Variant of the classic injury with placement of proximal clips on the cystic duct, but placement of the distal clips on the common duct. Division of the cystic duct between these two sites resulted in common duct obstruction, but biliary decompression through the free cystic duct stump.

Operative Management

One patient with a short common hepatic duct stricture and a continuous biliary system underwent biliary balloon dilatation with temporary stenting at ERCP and is awaiting further follow-up before a final decision about the need for surgery (Fig. 6). The patient with the anatomy depicted in Figure 4 simply had the common duct clip removed with oversewing of the cystic duct stump. The remaining patients underwent hepaticojejunostomy, with one of these anastomoses being made to the right hepatic duct only rather than to the common hepatic duct. The findings at the time of laparotomy supported the preoperative assessment in each case. Average operative time was 96 ± 5 minutes, and the average estimated blood loss was 184 ± 25 mL. A coronary "O" ring was placed routinely on the Roux segment and attached to the anterior abdominal wall to permit future percutaneous access to the anastomosis and biliary system, if necessary (Fig. 1C).

No complications occurred in the immediate postoperative period. Patients who had an elevation in serum bilirubin preoperatively had a decline to normal within 6 days after definitive surgery; the alkaline phosphatase was still abnormal, although decreasing at the time of hospital discharge in six of seven patients. The average length of hospitalization after hepaticojejunostomy was 9 days (range, 6 to 13 days). One of the patients developed cholangitis 4 months after hepaticojejunostomy and was found by CT scan to have mildly dilated intrahepatic biliary ducts. Retrograde percutaneous cholangiogram demonstrated debris at the anastomotic site, which was

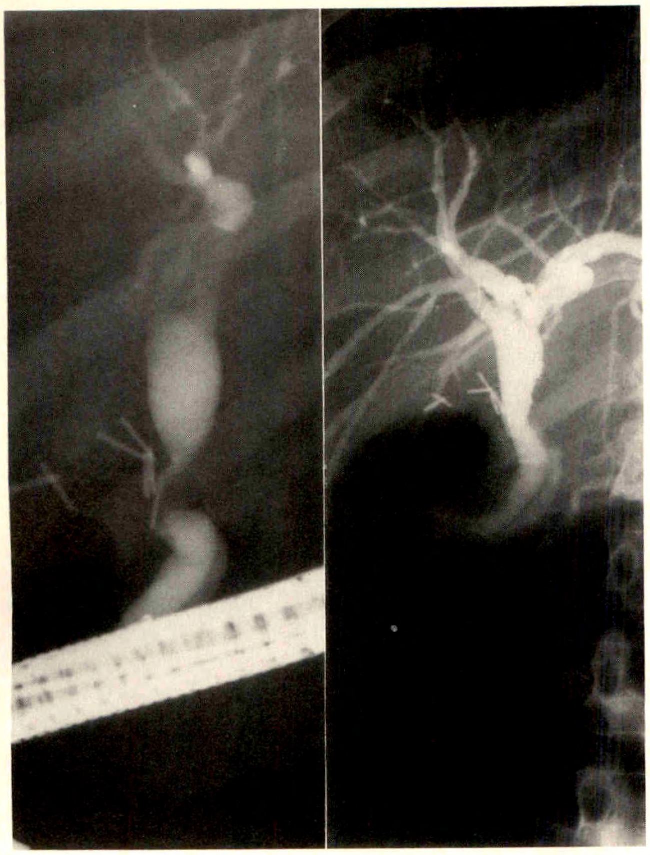


FIG. 6. Endoscopic retrograde cholangiograms showing (A, left) a common hepatic duct stricture and (B, right) the common hepatic duct after balloon dilatation.

removed by balloon catheter. A stent was placed across the anastomosis and removed after 3 weeks.

Discussion

Injury to the major biliary system after laparoscopic cholecystectomy caused two principle clinical manifestations: bile leakage into the abdomen with resultant pain and secondary bile peritonitis, and 2) biliary obstruction due to partial or complete hepatic or common duct ligation or late onset stricture.

Although it would clearly be better to recognize biliary injury at the time of laparoscopic cholecystectomy, the injury is likely to be unrecognized initially. Uncontrolled hemorrhage at the time of surgery should raise the suspicion of biliary injury and, if unusual measures are necessary to control the hemorrhage, particularly when there is inadequate visualization, burn or ischemic stricture of the common hepatic duct is possible. As with traditional, open procedures, technical aspects of the performance of the surgery appear to be important. Adequate visualization of the portal structures is essential. The cystic duct and artery should be identified clearly before ligation and division of any structures in the porta hepatis. Ideally, both the gallbladder–cystic duct and cystic duct–common duct junctions should be visualized and the surgeon should have a low threshold for cholangiography, particularly early in his experience, to help define the portal anatomy. Acute inflammation and chronic scarring of the gallbladder bed can restrict adequate identification of the anatomy, and early consideration of conversion to open cholecystectomy is important when the anatomy remains uncertain. During the hilar dissection, the cutting of a second distinct site along the duct should suggest the classic injury (Fig. 3). Finally, dissection away from the gallbladder neck toward the common duct, instead of the other direction, may help prevent the common duct from being mistaken for the cystic duct and subsequently being divided.

The classic pattern of laparoscopic injury appears to be misidentification of the common duct for the cystic duct, resection of a portion of the common and hepatic ducts, and an associated right hepatic arterial injury. A similar injury is known to occur with open cholecystectomy,[8] but not with the frequency or extent of hepatic duct resection. In addition, the operative videotapes with laparoscopic cholecystectomy provide an opportunity to determine definitively the mechanism of injury.

Although no single sign or symptom in the postoperative period was pathognomonic for ductal injury in this review, persistent patient complaints of diffuse abdominal pain should alert the physician to the possibility of a complication. One advantage of laparoscopic cholecystectomy should be that patients are relatively pain free after the procedure and, although there is much variability, complaints of severe or persistent pain should be carefully monitored and investigated early. Determination of serum alkaline phosphatase and total bilirubin are not particularly sensitive early in the initial postoperative course.

Three patients developed common hepatic duct strictures after laparoscopic cholecystectomy. Two presented 4 to 6 weeks after the initial procedure with jaundice and a completely obstructed duct, and the other returned 10 days after operation with diffuse abdominal pain and nausea, a slightly elevated serum alkaline phosphatase but normal total bilirubin, and was found to have a tight distal common duct stricture. The exact mechanisms for these injuries is not known for certain, but these strictures were probably caused by thermal injury or excessive manipulation of the common duct during the laparoscopic procedure. Smaller ducts may be particularly susceptible to stricture formation by these mechanisms. Therefore, judicious use of the laser or cautery during dissection in the portal region and minimizing the handling of the common duct cannot be overemphasized.

The principles of management of injuries sustained during laparoscopic cholecystectomy are essentially the same as for those sustained during open procedures. These include: early recognition of the injury, primary repair at the time of the initial laparoscopic procedure if possible, identification of the biliary anatomy before secondary operative repair, and Roux-en-Y hepaticojejunostomy unless there is a compelling reason not to do this. We have found preoperative percutaneous catheters to be particularly helpful at surgery for identification of the injured ducts and subsequent stenting if necessary, as well as preoperative CT drainage of intraperitoneal bile. Finally, intraoperative placement of a Roux-en-Y coronary "O" ring tacked to the anterior abdominal wall has been helpful in accessing the biliary system during postoperative follow-up. Most patients should have a successful result from hepaticojejunostomy unless there is technical difficulty, undiagnosed burn injury, or a divided duct is not incorporated into the hepaticojejunostomy.

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Laparoscopic Injuries to the Bile Duct

A Cause for Concern

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The authors report six patients who had injuries to their common hepatic bile duct at laparoscopic cholecystectomy over a 16-month period. Five of the six complications could be attributed to laser injuries during dissection in the region of Calot's triangle. The authors discuss the possible mechanism of these injuries, their perioperative management, and the methods of surgical reconstruction. The follow-up period ranges from 3 months to 21 months. Liver function parameters and isotope biliary excretion scans are back to normal in all six patients. The potential hazards of laparoscopic surgery demand that extraordinary care be used not only during the actual surgical procedure, but also in the preoperative decision concerning the dissection method to be employed.

THE MEDICAL COMMUNITY is experiencing a dramatic change in the way calculous disease of the biliary tract is treated. The recent revolution in minimally invasive surgery, specifically laparoscopic cholecystectomy, is still in progress. The rapid acceptance of, and the increasing demand for, the procedure is phenomenal when we consider that the benefits and risks of the procedure remain to be fully evaluated. It is unknown at present if laparoscopic methods can match the safety of the "gold standard" of an open cholecystectomy, or if the main benefit will be cost savings due to shortened hospital stay and rapid return to work.

Injuries to the bile ducts during cholecystectomy are not uncommon, occurring in approximately 0.5% of those undergoing open cholecystectomy.[1-3] With over 500,000 cholecystectomies performed annually for calculous disease in the United States, more than 2000 injuries can be expected annually with traditional methods of cholecystectomy.[4] What proportion of these cases will be performed laparoscopically in the future, and what rate of bile duct injury will be encountered with laparoscopic methods, are unresolved questions.

We report here our experiences with biliary reconstruction in six cases referred to our institution with high bile duct injuries after laparoscopic cholecystectomy over a 16-month period. We have previously suggested that coupling laser techniques with laparoscopic surgery for the beginner in both fields may be particularly dangerous.[5] For the description of biliary strictures, we have employed Bismuth classification based on the level of each stricture as it relates to the confluence of the hepatic duct (Fig. 1).

Case Reports

Case Study 1

A 57-year-old moderately obese woman underwent laparoscopic laser cholecystectomy for symptomatic gallstones. No technical problem was encountered during the procedure. Operative cholangiogram was not performed. Four days later, the patient developed abdominal pain and distention, with a mild fever and marginally elevated liver function parameters. Ultrasonography disclosed ascites with a large fluid collection in the subhepatic space. Laparotomy was performed, and a large-volume biliary ascites was evacuated. A subhepatic suction drain was placed and the patient developed a biliary fistula for about 3 weeks. The biliary drainage stopped for several days, and the drain was removed. The patient developed recurrent evidence of sepsis, and ultrasonography disclosed another subhepatic bile collection. This was drained percutaneously and, at the same time, a transhepatic catheter was placed in the biliary tree for proximal biliary diversion. The patient was managed nonoperatively for 4 further weeks and complained of multiple constitutional symptoms, including fatigue, nausea, and depression. About 11 weeks after the cholecystectomy, the patient was re-explored and reconstruction of a Bismuth type II stricture (Fig. 2) was undertaken with a hepaticojejunostomy Roux-en-Y anastomosis at the level of the hepatic duct bifurcation. All the liver function parameters returned to normal within 1 month of reconstruction. A Tc HIDA hepatobiliary scan performed 3 months later was totally normal.

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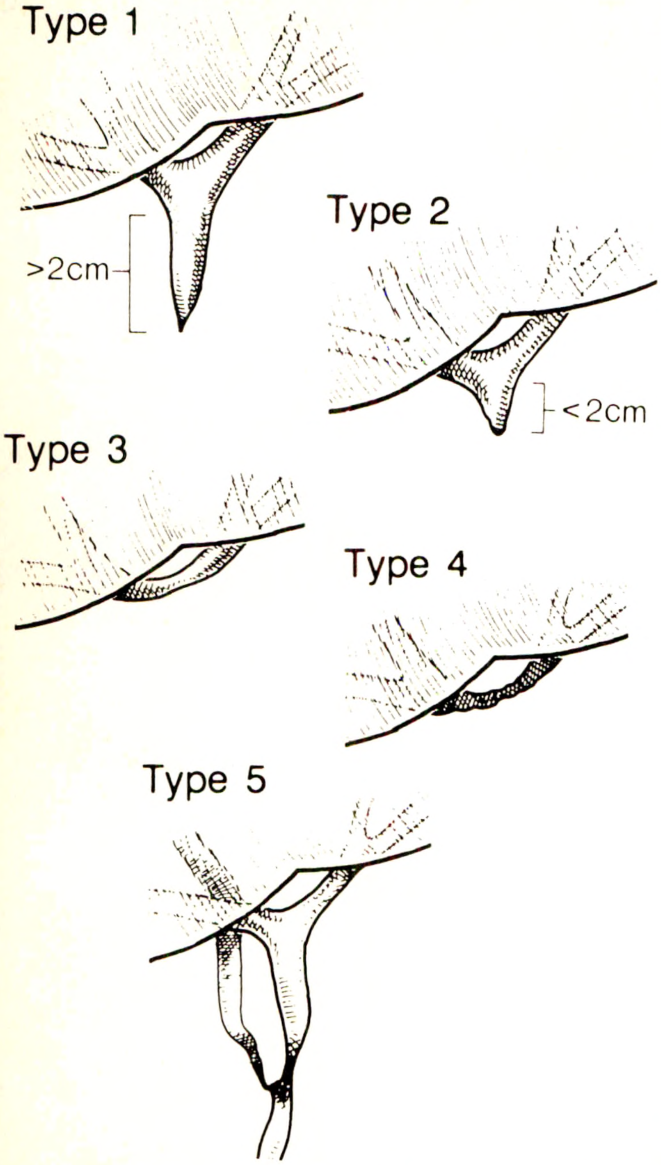

FIG. 1. Bismuth classification of benign bile duct strictures based on the location of the lesion in relation to the hepatic duct bifurcation Reprinted with permission from Blumgart et al.[18]

Case Study 2

A 58-year-old woman underwent laparoscopic laser cholecystectomy after a previous attack of mild acute cholecystitis. A moderate amount of adhesions was divided. Operative cholangiogram was attempted but failed. The cholecystectomy proceeded uneventfully.

Two days later, the patient developed evidence of a bile leak and underwent a laparotomy. The common bile duct was explored and a T-tube was placed. The patient then developed progressive mild jaundice, and a T-tube cholangiogram showed a Bismuth type II stricture proximal to the site of insertion of the T-tube (Fig. 3). Six weeks after the laparoscopic cholecystectomy, the patient was re-explored, and the Bismuth type II stricture was repaired by hepaticojejunostomy Roux-en-Y. All the liver function parameters returned to normal within 1 week. A Tc HIDA 3 months after the repair was also normal.

Case Study 3

A 43-year-old obese man underwent laparoscopic laser cholecystectomy for symptomatic gallstones. He remained well for 5 months, at which time he presented with progressive obstructive jaundice. Endoscopic retrograde cholangiopancreatography showed a stricture just below the common hepatic duct bifurcation. He underwent a percutaneous placement of a stent across the stricture. He remained relatively well for another 7 months, at which point he presented with an acute obstructive cholangitis. Percutaneous transhepatic cholangiogram showed a Bismuth type III stricture (Fig. 4). He underwent percutaneous transhepatic biliary drainage followed 4 days later by abdominal re-exploration. The stent was removed and a hepaticojejunostomy Roux-en-Y repair was performed at the hepatic duct bifurcation. Liver function parameters were completely normal at 1 month, and a Tc HIDA hepatobiliary scan performed 2 months later showed normal biliary excretion.

Case Study 4

A 38-year-old woman underwent laparoscopic laser cholecystectomy for asymptomatic gallstones. A subhepatic drain was placed and produced copious biliary drainage within 24 hours. The patient was immediately re-explored and was found to have a near-circumferential damage of the common hepatic duct just below its bifurcation. An end-to-end anastomosis was performed over a T-tube brought out through the distal duct. A T-tube cholangiogram performed 3 months later showed good healing of the anastomosis. The T-tube was accordingly removed. The patient remained asymptomatic for 2 months, but then presented with progressive obstructive jaundice. Endoscopic retrograde cholangiopancreatography was performed with attempted passage of a guide wire for possible stent placement, but this failed. A percutaneous transhepatic cholangiogram showed a Bismuth type IV (Fig. 5) stricture. The patient was re-explored, and the right hepatic duct as well as the confluence of the middle and left hepatic duct were anastomosed to a Roux-en-Y loop of jejunum. The patient's liver function parameters returned to normal within 3 weeks, and a Tc HIDA hepatobiliary scan performed 4 months later was totally normal.

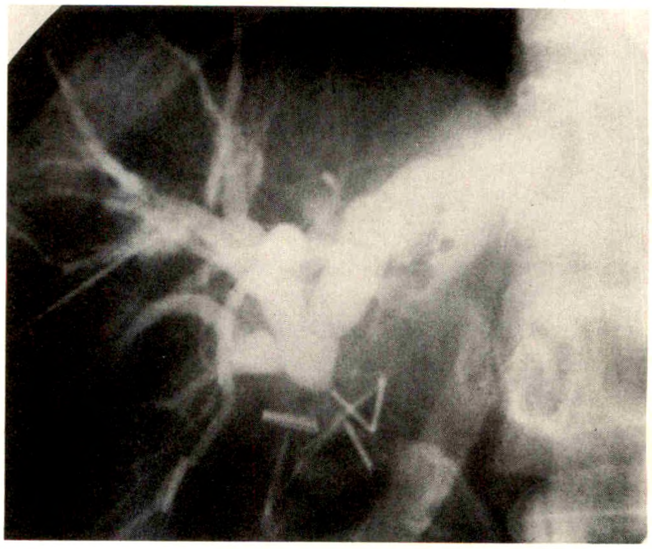

FIG. 2. Percutaneous transhepatic cholangiogram showing a Bismuth type II stricture. There is less than 2 cm of common hepatic duct below the bifurcation.

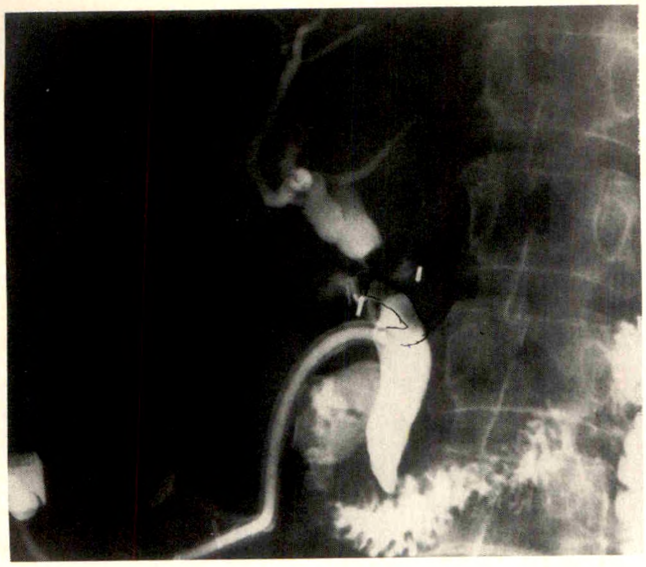

FIG. 3. T-tube cholangiogram showing a Bismuth type II stricture produced at laparoscopic cholecystectomy. Note that the T-tube was placed below the stricture at abdominal exploration.

Case Study 5

A 35-year-old woman underwent laparoscopic cholecystectomy for asymptomatic gallstones. Operative cholangiography was not performed. About 1 week after operation, she developed right upper quadrant pain, nausea, vomiting, and progressive jaundice. Percutaneous transhepatic cholangiogram disclosed a high duct bile duct stricture just below the level of the hepatic duct bifurcation. Two weeks later, she was re-explored, and the hepatic duct trifurcation was reanastomosed to a Roux-en-Y loop of jejunum. She made an uneventful postoperative recovery, and her liver function parameters became normal within 2 weeks. A Tc HIDA biliary scan performed at 3 months showed normal biliary drainage (Fig. 6).

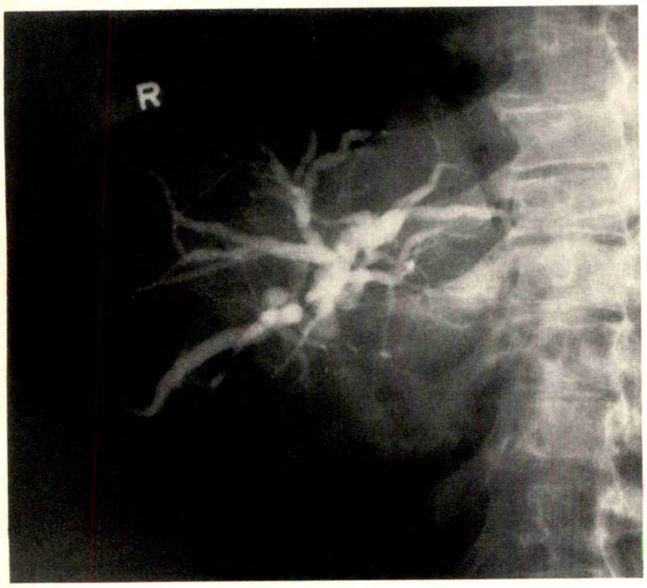

FIG. 4. Percutaneous transhepatic cholangiogram in a patient with obstructive cholangitis and a Bismuth type III stricture. Note that the metal stent that had previously been placed was totally occluded.

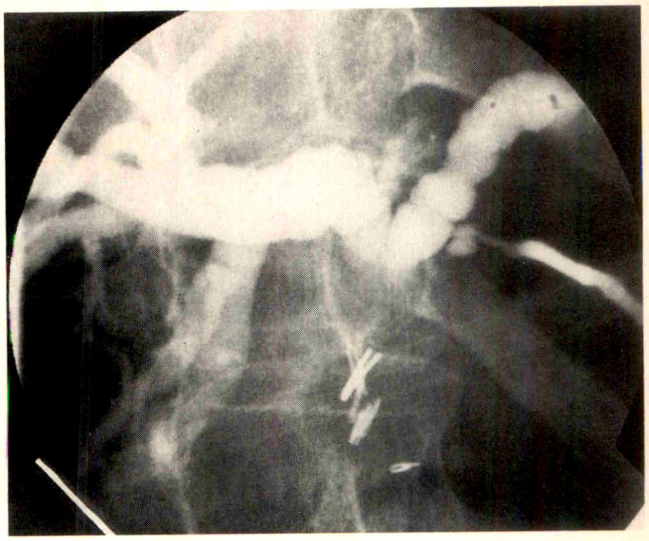

FIG. 5. Percutaneous transhepatic cholangiogram showing a Bismuth type III stricture. The hepatic duct bifurcation was intact, but there was no common hepatic duct remnant.

Case Study 6

A 71-year-old woman underwent laparoscopic laser cholecystectomy for symptomatic gallstones. Operative cholangiogram was not performed, but the operation proceeded uneventfully. The patient remained asymptomatic for 5 months, but re-presented with recurrent right upper quadrant pain with mild fever and mild elevation of liver enzymes. Ultrasonography showed a dilated intrahepatic ductal system. Percutaneous transhepatic cholangiogram confirmed intrahepatic duct dilatation and showed a long partial stricture of the distal two thirds of the common bile duct. The patient underwent a hepaticojejunostomy Roux-en-Y repair uneventfully. Liver enzymes were back to normal within 2 weeks of the reconstruction. A Tc HIDA scan at 6 months was normal.

Operative Details

Each exploration was notable for the presence of dense inflammatory reaction and fibrosis at the area of injury. There was a surprising finding of ductal tissue missing from the injured segment. No visible remnant of distal ductal tissue could be identified in two of the six cases, and the portal vein was easily identified as if it were an anterior structure in both instances. Healthy proximal ductal tissue was identified by dissecting inside the liver hilum and lowering the hilar plate as recommended by Bismuth. The mobilized proximal duct stump was trimmed of all scar tissue, and the biliary stoma was enlarged by incising into the left main duct. The largest possible biliary-enteric stoma was created by mucosa-to-mucosa approximation of the bile duct to a Roux-en-Y loop of jejunum in end-to-side fashion with interrupted 4–0 polyglycolic sutures. To avoid tension on the anastomosis,

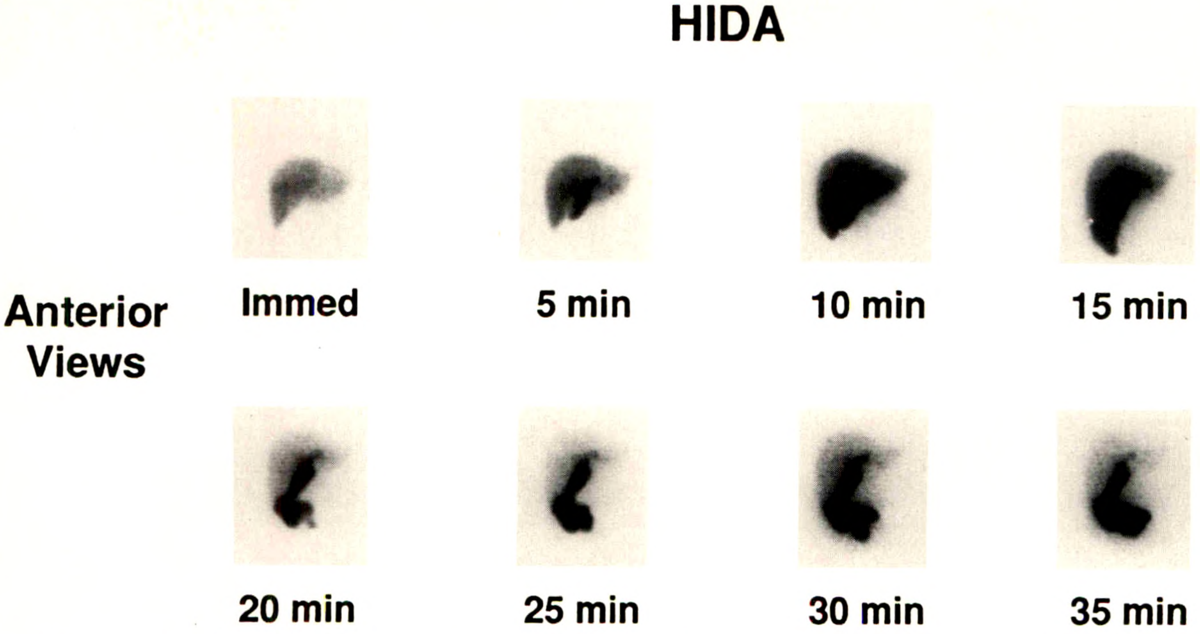

FIG. 6. Isotope biliary excretion scan with Tc-HIDA showing a widely patent and functioning hepaticojejunostomy at the level of the hepatic duct bifurcation.

the upper part of the jejunal loop was supported to the scar tissue of the gallbladder bed and the mobilized round ligament using multiple 3–0 silk sutures. Temporary (3 to 4 weeks) stenting of the anastomosis by the percutaneous transhepatic approach was employed in only two of the six individuals.

Comments

In the treatment of symptomatic cholelithiasis, the “gold standard” against which new techniques must be compared is an open cholecystectomy with intraoperative cholangiogram. In more than 100 years of experience with open cholecystectomy, the medical community has witnessed the evolution of acceptable morbidity and mortality rates with this procedure. A new standard may be set, however, as the tidal wave of enthusiasm and early experience with laparoscopic cholecystectomy methods develops. Public demand, coupled with wide acceptance of the laparoscopic technique, may well be so great that comparisons between “open” and “closed” cholecystectomy will be available only through the use of historical controls.

A recent report of 100 consecutive elective laparoscopic cholecystectomy indicates that only four patients required conversion to the “open” method. There were one minor bile duct injury, two postoperative bile leaks, and one clinical diagnosis of a retained common bile duct stone that passed spontaneously. The authors estimate a morbidity rate of 8% and a bile duct injury rate of 1% for laparoscopic cholecystectomy.[6] Clearly, the most serious worry is the issue of biliary tract injury, and our preliminary anecdotal experience suggests that the incidence may well be as high as 7% in institutions where multiple surgeons perform the “occasional” procedure without any individual obtaining a concentrated exposure. Institutions may be wise to initially limit privileges for laparoscopic surgery to a few surgeons with a genuine interest until the indications and contraindications are delineated and the safety of the procedure is well established.

It probably will be easier to scientifically evaluate the differences between various methods of laparoscopic dissection, namely, comparing laser with electrocoagulation methods. Such trials are already in progress.[7,8] Until the results of such comparisons become available, it will remain the domain of each individual surgeon (and patient) to choose the safest possible methodology. It is important to notice that the anatomic pattern of the laparoscopic injuries is identical to those inflicted at open cholecystectomy. The duct is damaged above the entrance of the cystic duct, presumably during dissection within Calot’s triangle.

Bile duct injuries during “open” cholecystectomy occur when 1) the wrong duct is ligated or transected, 2) the lumen of the bile duct is occluded during “flush ligation” of the cystic duct, 3) the blood supply to the duct is compromised by excessive dissection, and 4) the lumen of the duct is traumatized by manipulation or forceful “dilatation.”[9,10] To these four scenarios, we should now add a fifth possibility, namely, injury to ductal structures during inappropriate application and control of an energy source. From the practical viewpoint, the surgeon must be aware of the avoidable damage to ductal structures through inappropriate control of the "backstop effect" of laser dissection. Injuries at laparoscopic cholecystectomy attributable to inappropriate control of electrocautery is certainly possible, but as yet we have not encountered any.

Laser dissection methods rely on the ability of light energy to excite molecules within its path sufficient to cause heating of the recipient tissue and disruption of structural proteins.[11] During the 20-plus years of research into and experience with the methodology of laser surgery methodology, two adaptations have been used to limit unwanted tissue damage.

The wavelength of light energy can be chosen so that certain specific tissues are targeted. Practically, this applies only to the use of laser energy to disrupt calculi and leave its adjacent epithelium free of damage. Unfortunately, that wavelength most efficient in disrupting both pigmented and cholesterol stones is also the wavelength best absorbed (and heat producing) by bile as well.[11] The intermittent interruption of laser energy ("pulsed dye laser") also can be used to minimize thermal damage. This translates into delivering energy sufficient to disrupt biliary and urinary calculi while limiting damage to the surrounding epithelium.[12,13]

Modification of wavelengths and pulse variations, however, are unlikely to impact on the inadvertent injury to bile ducts caused by laparoscopic surgeons. This is because even the "smartest" laser is unlikely to be able to discriminate between the nearly identical physical characteristics of bile duct *versus* gallbladder (or other closely related important anatomic structures).

When laser mishaps occur, tissue damage probably is mediated by ischemic injury to the recipient structures. Moreover, the tissue coagulation effects of laser energy have been used in the welding-fusion of biliary tissues.[13–15] It is not surprising, therefore, that a misdirected laser beam can produce substantial and complex destructive injuries to ductal structures. The blood supply of the common bile duct is extremely variable. Two of our patients (Cases 3 and 6) presented a few months after an apparently successful cholecystectomy, and the strictures may well be attributed to ischemic injury. Whether the ischemia is due to a laser effect, or to excessive stripping and devascularization of the duct, or both, is impossible to determine.

Although anatomic variants are present in up to 15% to 20% of biliary cases, there was no indication in this series of referrals that such "anomalies" contributed to the resultant injuries. Operative cholangiography was attempted in only one of these six cases, and was successful in none. Omission of this step is potentially hazardous, especially when the visual perspective of the operating surgeon has been changed (and acutely so for those who are less experienced with laparoscopic methods). This is also particularly relevant because, laparoscopically, it is not conveniently possible to begin one's dissection at the fundus of the gallbladder, as has been described for avoiding injuries during "open" cholecystectomy.[1,4]

The level of experience of the operating surgeon and the technical difficulties at operation are other factors that can add to the risk of bile duct injury.[9,10] Each of our referred patients had relatively inexperienced surgeons (as is most of the surgical community to date). Two of the injured patients were described as obese at first operation. None, however, produced situations at operation that were perceived as dangerous enough to warrant conversion to an "open" procedure. The late Rodney Maingot, when talking about the operation of cholecystectomy, was both accurate and prophetic with the following two statements: 1) all complications are made in the operating room; and 2) the surgeon must operate by sight, not by faith.

It is interesting that, contrary to our customary patterns of referral, three of our six patients were referred for reconstructive surgical procedures by the primary surgeons.[9,10] The other three were referred first to interventional radiologists, and later were offered surgical repair. It may be that either surgeons are beginning to accept that benign strictures of the biliary ducts are best handled surgically[16–18] or that they prefer, with respect to their early experiences with laparoscopic cholecystectomy, to keep their "dirty laundry" within the surgical community.

The role of interventional radiology should not be minimized in the management of these patients. Percutaneous drainage of subhepatic bile collections is clearly preferable to a laparotomy. Percutaneous transhepatic cholangiogram is always performed ideally within 24 hours of the proposed reconstruction. It delineates the anatomy of the biliary tree proximal to the stricture and helps in the planning of a surgical strategy. The placement of a biliary catheter close to the hilum can be a useful guide in the tedious subhepatic dissection to locate a short proximal biliary stump. The catheter also can be used to temporarily stent the anastomosis if deemed desirable.

Our choice of surgical repair, a single-layer interrupted mucosa-to-mucosa anastomosis between bowel and bile duct, has in our hands and others[18,19] given superior results to all other techniques, including Rodney Smith's mucosal graft procedure. We recommend the method of direct mucosa-to-mucosa repair for those specialists who are challenged with these difficult situations. We no longer employ prolonged transhepatic intubation and stenting of the anastomosis as previously advocated for these high biliary strictures.[20]

Conclusions

We have recently successfully reconstructed the bile ducts of six patients who had injuries sustained at laparoscopic cholecystectomy. Five of these injuries were associated with laser dissection methods. Findings at operation were notable for the absence of substantial ductal length, and reconstruction at the level of the hilar liver plate was uniformly necessary.

We caution those who use laser methods of dissection during laparoscopic cholecystectomy to be particularly mindful of the "backstop effect" of laser energy, as well as the variations of ductal anatomy that can make for hazardous dissection. We believe that routine operative cholangiogram remains a major safeguard. It may be appropriate to learn laser and laparoscopic methods separately, only later to combine them if desirable, or alternatively, to await objective evaluation of the purported benefits of laser dissection techniques before subjecting patients to its potential risks.

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Addendum

Since the submission of this article, the authors have repaired nine additional similar bile duct injuries, and one patient has died of Candida sepsis.

Laparoscopic Cholangiography

Results and Indications

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One hundred sixty-five operative cholangiograms were attempted in 364 patients who underwent laparoscopic cholecystectomy (45%). Laparoscopic cholangiography was successful in 150 of 165 attempts (91%). Eighty-nine per cent of studies were normal (134/150) and 11% were abnormal (16/150). All 134 patients with normal cholangiograms remained asymptomatic (false-negative rate, 0%). False-positive studies occurred in 3 of 150 (2%) total cholangiograms and 3 of 12 (25%) abnormal cholangiograms consistent with choledocholithiasis. A total of 16 of 364 patients had proven common bile duct stones (4.4%). Eight of the sixteen stones were removed by preoperative endoscopic retrograde cholangiopancreatography/sphincterotomy. Five of sixteen stones were found at cholangiography, four of which were unsuspected (4/150, 2.6%). Retained common duct stones were found in 3 of 214 patients not undergoing cholangiography (1.4%). No complications or deaths occurred that were due to cholangiography. One biliary injury occurred (1/364, 0.3%), in a patient with aberrant anatomy who did not undergo cholangiography. Laparoscopic cholangiography is a safe technique with a success rate greater than 90%. Routine cholangiography is presently recommended for prevention of biliary injury, detection of stones in the cystic and common ducts, and for training purposes, especially during the learning phase of laparoscopic cholecystectomy.

THE RAPID DEVELOPMENT and growing acceptance of laparoscopic cholecystectomy has not been without controversy. One of the initial criticisms of the technique was the inability to perform operative cholangiography. A few publications during the past year have alluded to the technique of laparoscopic cholangiography.[1-5] Specific data regarding the accuracy, morbidity and mortality rates, false-positive and false-negative rates, and complications of laparoscopic cholangiography, however, are limited.

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The optimal type of cholangiography catheter, anatomic approach (cystic duct or direct gallbladder puncture), method of imaging (portable x-ray or fluoroscopy), and indications for laparoscopic cholangiography are also unresolved issues. The role of operative cholangiography is further confused by the use of alternative technologies such as preoperative intravenous cholangiography,[6,7] intraoperative lithotripsy,[8] and laparoscopic common bile duct exploration.[3] In addition, the role of perioperative endoscopic retrograde cholangiopancreatography (ERCP) is not well established.

The experience with laparoscopic cholangiography at the University of Maryland Medical Center is reviewed to define further its safety and efficacy, and to suggest a role for the operative cholangiogram in the management of the patient undergoing laparoscopic cholecystectomy.

Materials and Methods

Laparoscopic cholecystectomy was attempted in 384 consecutive patients at the University of Maryland Medical Center between September 1989 and January 1991. Twenty patients required intraoperative conversion to open cholecystectomy (5.2%) and were excluded from further analysis. The remaining 364 patients were included in this study. Patients who presented with evidence of choledocholithiasis, such as elevated serum bilirubin, dilated common bile duct, or common duct stones on abdominal ultrasound, underwent preoperative ERCP. Endoscopic sphincterotomy and stone extraction were performed if common duct stones were diagnosed.

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The decision to perform operative cholangiography was left to the discretion of the attending surgeon. Initially, the performance of cholangiography varied widely between surgeons, but the practice of routine cholangiography was gradually adopted over the course of the study period. Standard portable x-ray equipment was used in all cases; no studies were performed under fluoroscopic guidance. All studies were performed by direct cystic duct cholangiography, with the aid of a cholangiography fixation clamp (Cabot Medical Inc., Langhorne, PA). The clamp is a 5-mm diameter instrument with an atraumatic tip and hollow shaft, through which a polyethylene catheter may be inserted (Fig. 1). Direct puncture of the gall bladder or common bile duct to perform cholangiography was not used in this series. Cholangiography was not performed in patients with allergy to shellfish, iodine, or radiographic contrast material.

The cholangiogram was performed early during the procedure, immediately after dissection and identification of the cystic duct. The junction of the cystic duct and gallbladder was determined and a single 9-mm surgical clip was applied to the duct just below the gallbladder neck. The grasper used to retract the neck of the gallbladder was removed from the midclavicular port and reapplied through the epigastric port. Curved laparoscopic microscissors were inserted into the now vacant midclavicular port and used to create an opening in the duct. The cholangiography fixation clamp, inserted through the same midclavicular port, was used to direct, insert, and secure the cholangiogram catheter in the cystic duct (Fig. 2). All grasping forceps and nonessential metal instruments were removed from the operative field. Approximately 10 mL half-strength iodinated contrast material was injected slowly, and a standard portable radiograph was obtained. The procedure was repeated, if necessary, until an adequate cholangiogram was obtained. The technique of laparoscopic cholangiography was recently described in detail.[9]

Results of Cholangiography

Laparoscopic cholangiography was attempted in 165/364 (45%) of patients who underwent laparoscopic cholecystectomy. Operative cholangiography was not attempted in 199/364 (55%) cases, for the reasons listed in Table 1. The surgical expertise and instrumentation needed to easily perform a cholangiogram was not available during the first 74 cases, so a more accurate approximation of the rate of attempted cholangiography in this series is 165/290 patients (57%).

Cholangiography was performed in 141 of 340 (38%) patients with a diagnosis of symptomatic cholelithiasis, 6 of 17 (41%) patients with acute cholecystitis, and 3 of 7 (43%) patients with biliary pancreatitis (Table 2). The other four patients with biliary pancreatitis had preoperative cholangiography by ERCP.

Results

Cholangiography was successful in 150 of 165 (91%) attempts and unsuccessful in 15 of 165 (9%) attempts. Reasons for failure included inability to cannulate the cystic duct in 11 cases and contrast extravasation in four cases. No attempts at cholangiography by direct puncture of the gallbladder or common bile duct were made in cases where cystic duct cholangiography was unsuccessful.

Operative cholangiograms were interpreted as normal in 134 of 150 cases (89%). None of these patients have required treatment for retained common duct stones dur-

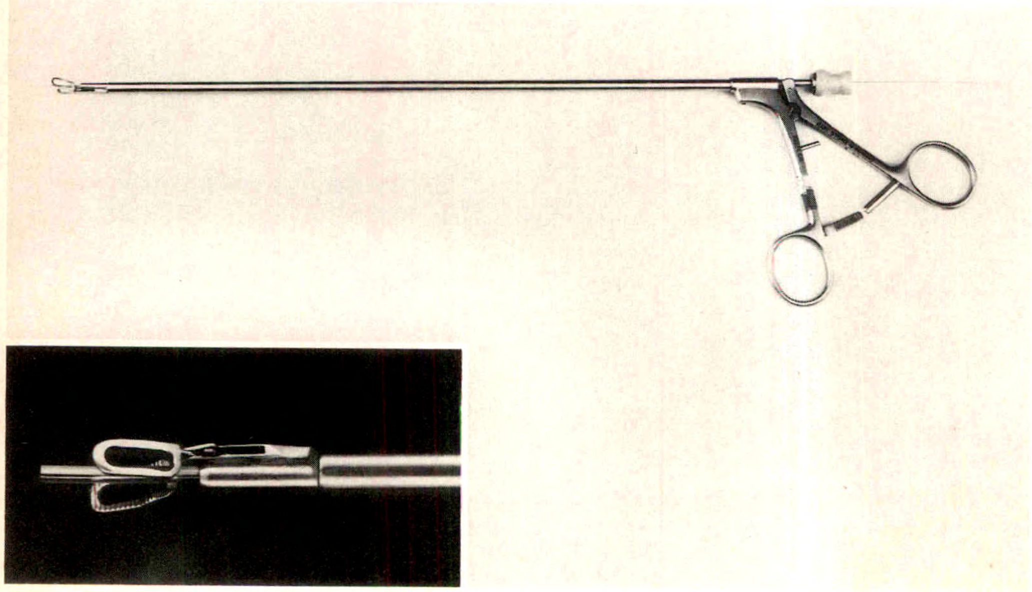

FIG. 1. Cholangiography fixation clamp, with inset showing close-up view of clamp tip and protruding catheter tip.

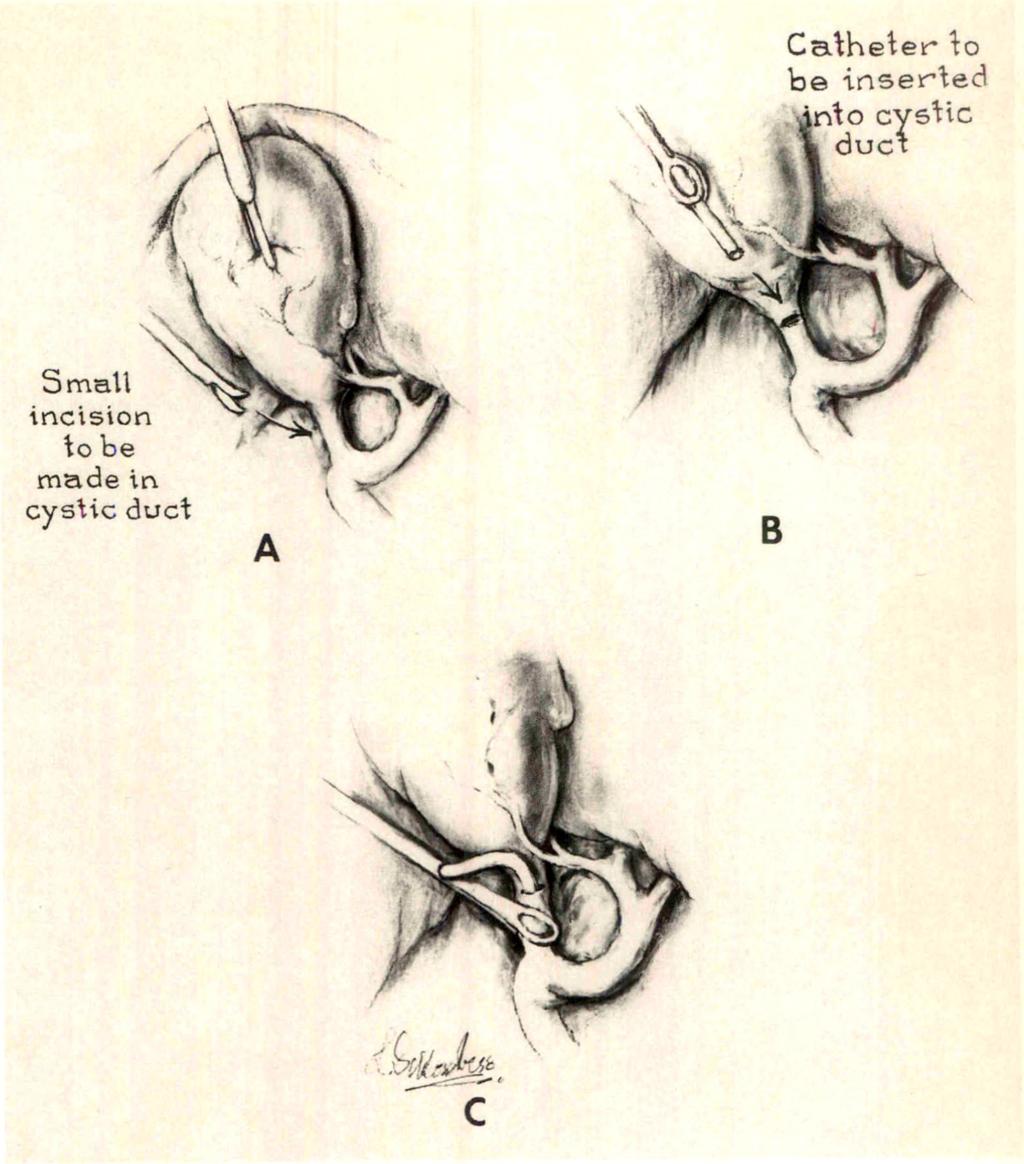
Small incision to be made in cystic duct
A
Catheter to be inserted into cystic duct
B
C

FIG. 2. Primary steps of cystic duct cholangiography, including (A) cystic duct incision, (B) guidance of cholangiography catheter into the duct, and (C) securing of the catheter with the cholangiography clamp.

ing the follow-up period (range, 3 to 15 months), for a false-negative rate of 0%.

Of 150 cholangiograms, 16 (11%) were interpreted as abnormal. Four of the sixteen abnormal studies showed aberrant biliary anatomy of clinical significance, but no evidence of choledocholithiasis. All four patients have remained asymptomatic. The remaining 12 of 16 abnormal cholangiograms showed evidence of filling defects in the extrahepatic biliary tree. Six of the 12 studies with filling defects were thought to be strongly consistent with cho-

TABLE 1. *Reasons for Omission of Cholangiography*

Indication	No.	(%)
Technology unavailable	74	37
Study not indicated	61	31
No reason given	30	15
Short cystic duct	13	6
Preoperative endoscopic retrograde cholangiopancreatography	9	5
Contrast allergy	8	4
Purulent bile	3	1.5
Cystic duct necrosis	1	0.5
Total	199	100

TABLE 2. *Performance of Cholangiography According to Diagnosis*

Diagnosis	No. of Cholangiograms	No. of Patients	(%)
Symptomatic cholelithiasis	141	340	38
Acute cholecystitis	6	17	41
Biliary pancreatitis	3*	7	43
Total	150	364	41

* The four patients who did not receive cholangiograms underwent preoperative endoscopic retrograde cholangiopancreatography.

ledocholithiasis. These studies showed ductal dilation, single or multiple irregular defects, or obstruction to the flow of contrast. The remaining six of 12 studies with filling defects were considered equivocal. These studies showed normal-caliber bile ducts with free flow of contrast into the duodenum, but small filling defects (1 to 2 mm) consistent with either small stones or air bubbles.

Five of the six patients with cholangiograms strongly suspicious for choledocholithiasis had removal of common duct stones. Four patients had postoperative ERCP and sphincterotomy and one had open common duct exploration immediately after laparoscopic operative cholangiography. The sixth patient refused postoperative ERCP, and has remained asymptomatic at 13 months' follow-up.

The six patients with equivocal studies were observed. Three of these six patients underwent postoperative ERCP for recurrent pain (Two of three also had mild nonspecific elevation of hepatic transaminases); all three ERCPs were normal. A total of 3 of 12 intraoperative cholangiograms with filling defects were subsequently proven normal at ERCP. The false-positive rate for cholangiograms suspicious for choledocholithiasis is therefore 25%. The false-positive rate for all cholangiograms is 3 of 150 (2%).

Three patients with abnormal cholangiograms had filling defects located in the cystic duct. Stones were extracted intraoperatively in 2 patients. The third patient had an attempt at operative extraction, but no stone was found. A repeat cholangiogram failed to show the filling defect, so the patient was observed. She subsequently required ERCP and sphincterotomy for a common bile duct stone. The cholangiography results and clinical outcome of all patients in the series are summarized in Figure 3.

Management of Choledocholithiasis

Proven common bile duct stones were found in a total of 16 of 364 patients (4.4%) (Table 3). Eight of sixteen cases were suspected preoperatively and stones removed by ERCP and sphincterotomy. Five cases were discovered by operative cholangiography. Four of these cases were unsuspected (4/150, 2.6%), and the fifth was suspicious for choledocholithiasis but had an unsuccessful attempt at biliary cannulation during preoperative ERCP. The subsequent laparoscopic operative cholangiogram detected a common duct stone, which was removed during the same procedure by open common duct exploration. Three of sixteen common duct stones were recognized postoperatively in patients who did not receive operative

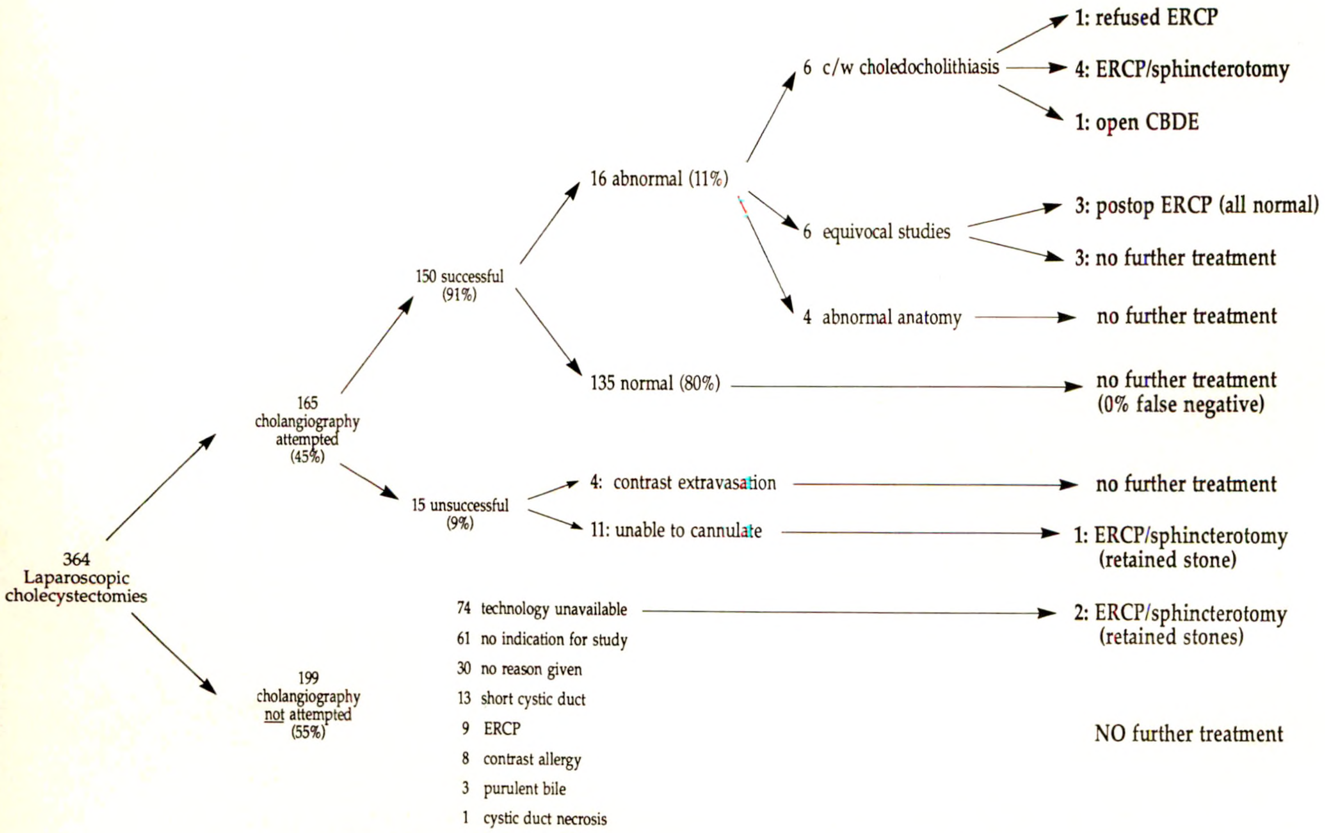

FIG. 3. Flow chart showing cholangiography data and outcome for all patients.

TABLE 3. *Detection and Treatment of Choledocholithiasis*

Method	No.	(%)
Preoperative endoscopic retrograde cholangiopancreatography	8	50
Operative cholangiography		
Unsuspected	4	25
Suspected	1*	6
Postoperative endoscopic retrograde cholangiopancreatography	3	19
Total	16†	100

* This patient had elevated bilirubin and transaminase levels, with a failed attempt at endoscopic retrograde cholangiopancreatography before operation. Operative cholangiography findings were positive, and an open common duct exploration was performed.

† Total incidence of common duct stones was 16 of 364 (4.4%).

TABLE 4. *Results of Endoscopic Retrograde Cholangiopancreatography*

	Before Operation	After Operation
Total no. of studies	20	15
No. of studies positive for common bile duct stones (%)	8 (40%)	9 (60%)

cholangiograms. The last three cases represent retained common duct stones, which occurred in 3 of 214 patients (1.4%) in the group who did not receive a cholangiogram.

Perioperative ERCP

Endoscopic retrograde cholangiopancreatoraphy was performed in 35 of 364 (9.6%) of patients undergoing laparoscopic cholecystectomy (Table 4). The study was performed preoperatively in 20 patients and postoperatively in 15 patients. Eight of the twenty preoperative studies performed to exclude the presence of common bile duct stones were positive (40%), and 9 of 15 studies performed postoperatively showed evidence of choledocholithiasis (60%). One failed attempt at preoperative ERCP occurred in the series, in the patient described above. All other attempts at endoscopic stone extraction, both preoperative and postoperative, were successful. There was one complication related to the performance of ERCP (1/35, 2.9%). A mild case of pancreatitis occurred in a patient after postoperative ERCP and sphincterotomy, which required hospitalization with intravenous hydration and bowel rest for 48 hours. The patient recovered without further sequelae. No complications occurred as a result of the three normal ERCPs performed in patients with equivocal intraoperative cholangiograms.

Operative Time and Cost

Operative times were 96 ± 8 minutes in patients not undergoing cholangiography and 116 ± 15 minutes in patients who received an operative cholangiogram. The actual time necessary to perform individual cholangiograms was not recorded prospectively, so the cholangiography time was approximated as the difference between the mean operative times of patients who received cholangiograms and those who did not. The difference between these times translates into an average of 20 minutes for the performance of cholangiography. The average cost for an operative cholangiogram was computed based on this time of 20 minutes for cholangiography. Components of the total patient cost include the operative time ($7 per minute), the anesthesiologist's fee, and the radiology fees. Anesthesia fees were calculated for 20 minutes of operating time in a relatively healthy patient (ASA class I or II). The radiology component included a professional interpretation fee and a technical fee to cover the cost of film and the technician to perform the radiograph. The average patient cost was calculated as the sum of these individual costs, or $299.50 (Table 5).

Discussion

The subject of operative cholangiography has generated considerable interest and controversy since its inception in 1932.[10] Equally enthusiastic supporters may be found for both routine and selective performance of operative cholangiography. The weight of evidence in the current literature seems to support a policy of selective cholangiography during "open" cholecystectomy.[11-14] The rapid development and widespread acceptance of laparoscopic cholecystectomy, however, has caused the controversy surrounding operative cholangiography to resurface.

Factors inherent with two-dimensional, video-directed surgery may alter the surgeon's approach to the biliary tract. Laparoscopic removal of the gallbladder takes away the surgeon's three-dimensional perspective, eliminates tactile clues, and limits the ability to provide exposure of the operative field. When combined with unfamiliar instrumentation and lack of experience, the surgeon may be hesitant to venture near the common duct. This may impair the ability to identify safely the distal cystic duct

TABLE 5. *Cost of Operative Cholangiography*

Item	Cost ($)
Anesthesiology	48.00
Operating room time ($7/min)	140.00
Radiologic fees	
Technical fee	61.50
Interpretation fee	50.00
Total	$299.50

All costs are based on cholangiography time of 20 minutes and patient ASA class I or II.

and common bile duct, especially during the learning phase of laparoscopic cholecystectomy. Operative cholangiography provides an accurate "road map" to define the pertinent anatomy and minimize risk of injury.

The routine use of cholangiography also may be useful to delineate abnormal biliary anatomy. Aberrant or unusual anatomy of clinical significance occurs in 6% to 8% of cholecystectomies,[15] and was detected in 2.6% (4/150) of patients in this series. The only biliary injury in the present series occurred in a patient with aberrant anatomy, with the cystic duct inserting into the right hepatic duct (Fig. 4). The injury occurred before the availability of cholangiography, and may have been prevented had a cholangiogram been performed. Obviously, it is not possible to determine the number of injuries prevented by routine operative cholangiography in the absence of data from a controlled, prospective trial. Until the exact incidence of operative biliary injury and late stricture formation during laparoscopic cholecystectomy is clearly documented, routine use of cholangiography may be recommended.

Another potential advantage of routine operative cholangiography is the immediate detection of biliary injury when it occurs. This approach may decrease the morbidity and mortality rates resulting from delayed diagnosis. Some critics refute the contention that routine cholangiography prevents biliary injury with the observation that many surgeons proceed with gallbladder dissection while awaiting development of the cholangiogram.[16] Any advantage of defining the exact biliary anatomy would obviously be eliminated by this technique. Unlike open cholecystectomy, dissection of the gallbladder from the liver does not usually proceed while awaiting the development of the film during laparoscopic cholecystectomy. In addition, some surgeons advocate complete dissection of the gallbladder away from the liver bed before cystic duct transection, to insure correct identification of ductal structures.[7] This is a difficult maneuver to accomplish during laparoscopic cholecystectomy. Routine performance of cholangiography may help to overcome these limitations of laparoscopic cholecystectomy and make inadvertent injury to unrecognized or aberrant ductal structures less likely.

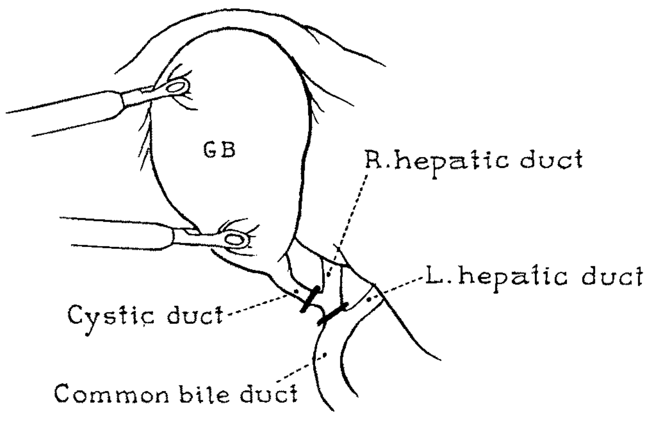

FIG. 4. Diagram of operative biliary injury that occurred as a result of inadvertent ligation of the right hepatic duct.

The role of laparoscopic cholangiography for the detection of unsuspected common bile duct stones is less clear. Patients at risk for choledocholithiasis are evaluated and treated preoperatively, because laparoscopic surgical options for the treatment of choledocholithiasis are limited at present. The development of laparoscopic common bile duct exploration may eventually change this approach.[3] The fact that "high-risk" patients are screened and treated with ERCP before cholecystectomy makes it impossible to draw conclusions regarding the efficacy of laparoscopic cholangiography in detecting common bile duct stones from this data. The incidence of unsuspected common bile duct stones discovered during cholangiography in this series is 4 of 150 patients (2.6%), consistent with that published in other series of laparoscopic (3% to 7%) and open (5% to 10%) cholecystectomies.[13,18-20]

An additional benefit of routine cholangiography is the detection of stones in the cystic duct. Three patients had stones present in the distal cystic duct. Although the natural history of stones left in the cystic duct is not clear, at least one patient in the series required postoperative ERCP and extraction of a cystic duct stone that apparently migrated into the common bile duct. The lack of ability to palpate the duct and the frequent uncertainty about the exact length of the cystic duct during laparoscopic cholecystectomy are obviated by performance of a cholangiogram. The hesitancy to dissect near the common duct is likely to become less of an issue as the technical skills of surgeons increase, illustrated by the recent report of a series of laparoscopic common bile duct explorations.[3]

The total incidence of known common bile duct stones in this series is only 4.6%, which is somewhat lower than the usually quoted figure of 8% to 13%.[21] This figure may reflect our early referral pattern of patients at low risk for choledocholithiasis.[22] These patients presented almost exclusively with mild to moderate symptomatic cholelithiasis. Only 7 of the first 200 patients (3.5%) in our series had abnormal biochemical testing or abdominal ultrasound results (except for the presence of cholelithiasis), placing them at low risk for the presence of common duct stones. The incidence of common duct stones in our last 184 patients is nearly 10% (unpublished data).

Other reasons for the routine performance of laparoscopic cholangiography relate to the development of the skills necessary to perform the study. Even opponents of routine laparoscopic cholangiography acknowledge that the ability to perform a cholangiogram is necessary.[23] Current data suggest that some "learning curve" is present;

one recent series required the performance of 37 cholangiograms before completion of the study was routinely successful.[24] It is desirable to develop the technique on easier cases so that the likelihood of success is increased when cholangiography is necessary in a difficult situation. Recent data suggest that the successful cannulation rate may be lower in institutions where cholangiography is performed infrequently. The failure rate in 1518 collected patients reported by the Southern Surgeons Club (where the majority of surgeons practice selective laparoscopic cholangiography) is 23%,[25] whereas failure rates from large series where routine laparoscopic cholangiography is performed are less, in the range of 6% to 10%.[2,26] The unsuccessful cannulation rate in this series is 9%, in agreement with these data. An additional consideration is the training of surgical residents. Routine cholangiography insures that each resident that completes training in laparoscopic cholecystectomy also will be competent in laparoscopic cholangiography. Training issues such as these have recently stimulated interest in the surgical literature.[27]

Reasons against the use of routine cholangiography include increased operative time, expense, risk of biliary injury, low yield of unsuspected common duct stones, and a concern over an increased risk of false-positive studies, leading to unnecessary common bile duct exploration or ERCP.

The present data show an increase in operative time of 20 minutes in cases where an operative cholangiogram is performed. It was assumed that this time difference was due primarily to the performance of the cholangiogram. Because this value was obtained from retrospective analysis, it is subject to inherent selection bias. The level of difficulty of the dissection and surgeon experience were not controlled factors. This value, however, is consistent with estimates of the time necessary to obtain an open operative cholangiogram at our institution. The gradual adoption of routine cholangiography during the second half of the study should help to minimize this bias.

The estimated patient cost of an individual cholangiogram in this series is $299.50. Forty-seven per cent of that cost is due to operating room time. The use of fluoroscopic imaging equipment has been shown to substantially reduce that time,[1] and may help to control cost. However, routine fluoroscopic capability is not readily available to many general surgeons at present.

Laparoscopic cholangiography appears to be a safe technique. In several published series to date, no biliary injury or other complications have been attributed to the performance of a cholangiogram.[1-5,18] One hundred fifty studies without complication are reported in this series.

False-positive rates as high as 29% have been recently reported during open cholecystectomy,[28] although more commonly accepted rates are 3% to 10%.[14,16,29] The false-positive rate in this series is 2% for all studies and 25% for the 12 abnormal studies.

The primary concern over a false-positive cholangiogram during open cholecystectomy is that it may result in an unnecessary common bile duct exploration. Using our treatment algorithm, the result of a false-positive laparoscopic cholangiogram is the performance of an unnecessary diagnostic ERCP. Although ERCP is not a trivial procedure, the morbidity and mortality rates of diagnostic ERCP are considerably lower than those of common bile duct exploration.[30-34] No complications arose from the three unnecessary ERCPs performed in this series. The incidence of false-positive cholangiograms during laparoscopic cholecystectomy should ultimately approach that during open cholecystectomy because there are no inherent differences between open and laparoscopic cholangiography except for the use of a clamp to direct and secure the catheter in the cystic duct. Good operative technique and careful attention to detail are critical.

The authors currently advocate routine cholangiography during laparoscopic cholecystectomy despite the acknowledged increase in both operative time and cost. The benefits obtained from clarification of biliary anatomy, detection of cystic and common bile duct stones, and issues of training may outweigh these disadvantages.

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Donor Hyperglycemia as a Minor Risk Factor and Immunologic Variables as Major Risk Factors for Pancreas Allograft Loss in a Multivariate Analysis of a Single Institution's Experience

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The impact of multiple donor and recipient variables on functional survival of 307 cadaveric pancreas allografts transplanted in 253 recipients at the authors' institution between July 25, 1978 and September 4, 1990 was determined using the Cox proportional hazards regression model. Relative risk of graft loss was calculated for all cases as well as for technically successful (TS) ones. Factors with an impact in descending order of significance for TS cases were immunosuppression (RR = 3.9 for double-drug *versus* triple-drug maintenance, $p < 0.0001$); recipient category (RR = 2.4 for pancreas alone *versus* simultaneous pancreas/kidney, $p = 0.009$); retransplantation (RR = 1.8 for retransplants *versus* primary grafts, $p = 0.007$); donor hyperglycemia (RR = 1.7 for blood glucose ≥ 200 *versus* < 200mg/dL, $p = 0.02$); human leukocyte antigen (HLA) matching (RR = 2.1 for poor *versus* a good match, $p = 0.04$). A logistic regression analysis also was performed to determine which factors predisposed to technical failure; none were identified. To make the model as relevant as possible to their current program, the authors analyzed only the bladder-drained cases (n = 221; 1984 to 1990). All patients received triple therapy. Recipient category, retransplantation, donor hyperglycemia, and degree of HLA matching remained as significant risk factors. Construction of estimated survival curves showed that the results of retransplantation were significantly improved, and the penalty incurred by using hyperglycemic donors was partially ameliorated by using well-matched donors. Because preservation times up to 30 hours did not exert an adverse effect on outcome, an argument is made to share pancreata between centers to achieve good matches.

THE RESULTS OF pancreas transplantation have continuously improved during the past decade.[1] Factors seemingly associated with this improvement include a reduction in technical complications,[2] more effective immunosuppression by combination drug therapy,[3] and earlier diagnosis and treatment of rejection episodes, either by monitoring the kidney in synchronous transplants[4] or by measuring the enzyme activity of graft exocrine secretions,[5] which is made possible by a temporary catheter[6,7] or continuously by urinary drainage into the bladder.[8] In addition, data from the Pancreas Transplant Registry,[1,9] as well as from our own experience at the University of Minnesota,[10] show graft survival rates to be higher in recipients who are matched than in those who are mismatched for donor antigens at the human leukocyte antigen (HLA)-DR locus.

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The influence on pancreas transplant outcome of variables such as hyperglycemia, hyperamylasemia, need for dopamine, age, and other possible risk factors have not been extensively studied, although a previous univariate analysis of the University of Minnesota experience suggested that donor hyperglycemia was associated with decreased long-term pancreatic allograft survival.[11] In the analysis presented here, we used the Cox proportional hazards regression model to determine the prognostic significance of these and other factors for pancreas transplant outcome at a single institution.

Materials and Methods

Patients, Techniques, and Management

The 307 cadaver donor pancreas transplants performed in 253 recipients at the University of Minnesota Hospital between July 25, 1978 and September 4, 1990 provided the material for analysis. Descriptions of the patient demographics, surgical techniques, methods of graft preservation, and immunosuppressive regimens have been provided in other publications,[12-14] and only the salient details are briefly reiterated here.

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Forty-six of the donor pancreata were segmental, and 251 were either whole or whole pancreaticoduodenal grafts. One hundred twenty-two cadaver pancreas grafts were procured from donors who also gave livers.

Before 1983, pancreas grafts were transplanted immediately after completion of the donor operation. Since 1983, cadaver grafts have been preserved by cold storage[14] in either silica-gel-filtered plasma solution (n = 180) or the University of Wisconsin (UW) solution (n = 108) for 4 to 38 hours (mean, 16.4 ± 6.8 hours).

The recipients were classified into three categories: a pancreas transplant alone (PTA, n = 113), a pancreas after a kidney transplant (PAK, n = 94), and a simultaneous pancreas and kidney transplant (SPK, n = 99). In addition, one patient received a simultaneous pancreas and liver transplant. Patients who received more than one pancreas transplant could be in one category for their primary grafts and another for their retransplants.

Management of the graft pancreatic duct by order of introduction into our series was by free drainage into the peritoneal cavity (open duct) in 10, ligation in 3, duct injection in 35, enteric drainage in 38, and bladder drainage in 221. Between November 1984 and July 1986, a prospective comparison of enteric and bladder drainage was conducted.[13] Since that time, the bladder drainage technique has been used almost exclusively, except for special situations, such as in patients diabetic as a consequence of total pancreatectomy, in which case enteric drainage was used to correct exocrine as well as endocrine deficiency.[15] Again, patients who received a first transplant by one technique could receive a subsequent transplant by another technique.

A variety of immunosuppressive regimens have been used, reflecting the advances that have been made during the period studied. Azathioprine and prednisone were used for maintenance immunosuppression in all cases from 1978 to 1981, whereas cyclosporine and prednisone were used for this purpose from 1981 to 1983. Beginning in 1983, cyclosporine, azathioprine, and prednisone were used in combination (triple therapy).[16] Before July 1986, Minnesota antilymphocyte globulin (ALG) was used only in recipients of cadaver pancreas transplants alone. Since 1986, all recipients of solitary pancreas transplants (PTA or PAK) have been given 20 mg/kg/day ALG for 7 to 14 doses, as were all SPK recipients until 1988. Since 1988, SPK recipients have been randomized to induction with either OKT3 (5 mg/dose for 7 to 14 doses) or ALG as part of a study that also includes recipients of cadaver kidney transplants alone.

Statistical Analysis

Univariate Analysis. Patient and graft survival rates were calculated by the actuarial method. Grafts were considered functioning as long as the recipients were insulin independent. Graft loss was defined as resumption of exogenous insulin for whatever reason, or death with a functioning graft. Graft survival rates were calculated for all and for technically successful (TS) cases. In addition, separate analyses were conducted of all and of only the technically successful bladder drained cases between 1984 and 1990. Grafts lost for nonimmunologic reasons, such as thrombosis, infection, bleeding, or pancreatitis were defined as technical failures (TF).

The probability that a difference between actuarial survival rate curves of recipient groups according to a single variable was due to chance alone was calculated by the Gehan variant of the generalized Wilcoxon test.[17] P values less than 0.05 were considered statistically significant.

Multivariate Analysis. The proportional hazards regression model of Cox[18] was used to simultaneously determine the significance of several variables in both the donor and recipient on graft survival and the relative risk for graft loss based on these factors. The BMDP statistical package[19] was employed to fit the regression model, and log hazard plots were constructed to ensure that model assumptions were satisfied. The variables included are described in the Results section.

Results

Analysis of Cadaver Donor Grafts: All Techniques

The analyses presented in this section of the influence of both donor and recipient factors on outcome are inclusive of the entire series of cadaveric pancreas transplants performed from 1978 to September 1990, regardless of duct management method. Separate analyses of all cases and of technically successful cases were performed in both the univariate and multivariate limbs of these studies.

Univariate Analysis. In accordance with our previous report,[11] donor hyperglycemia (glucose ≥ 200 mg/dL) was associated with a significantly lower graft functional survival rate, and this was true whether all or only TS cases were analyzed (Table 1). Functional survival was also longer when the pancreas was procured from donors that also gave a liver. This is likely an era effect (Table 2), because the combined procedure was performed only sporadically before 1985, whereas it became routine after that time.

Similarly, the apparent improved survival of grafts that were preserved for 24 to 30 hours as opposed to less than 24 hours is an era effect, because early on in our series grafts were transplanted immediately after procurement. The same explanation may apply to the trend toward improved survival observed with pancreata preserved with UW solution because that solution was only used later in the series.

TABLE 1. *Univariate Analysis of Donor Factors That Influence Pancreas Allograft Survival: All Cadaver Donor Cases*

	% 1-yr Graft Survival	
Donor Factor	All Cases	TS Cases
Glucose		
<200 mg/dL	57 (n = 124) p = 0.01	71 (n = 97) p = 0.002
≥200 mg/dL	40 (n = 164)	48 (n = 132)
Liver also procured		
Yes	58 (n = 122) p = 0.0004	69 (n = 100) p = 0.0004
No	38 (n = 183)	53 (n = 145)
Preservation time (hr)		
<24	49 (n = 244) } p = 0.09	61 (n = 192)
24–30	66 (n = 27)	70 (n = 24) p = 0.56
>30	33 (n = 6) } p = 0.08	50 (n = 4)
Preservation solution		
UW	58 (n = 106) p = 0.07	69 (n = 88) p = 0.08
Plasma based	47 (n = 167)	58 (n = 130)
A, B mismatch		
0	77 (n = 18) 0 *vs.* 2; p = 0.02	81 (n = 17) 0 *vs.* 2; p = 0.04
1	47 (n = 40) 0 *vs.* 3; p = 0.03	56 (n = 34) 0 *vs.* 3; p = 0.07
2	43 (n = 83) 0 *vs.* 4; p = 0.05	49 (n = 68) 2 *vs.* 4; p = 0.06
3	44 (n = 53)	54 (n = 76) 3 *vs.* 4; p = 0.04
4	51 (n = 69)	70 (n = 49)
DR mismatch		
0	53 (n = 56) 0 *vs.* 2; p = 0.05	57 (n = 50)
1	54 (n = 153)	68 (n = 119) 1 *vs.* 2; p = 0.007
2	38 (n = 88)	47 (n = 71)
Amylase (IU/L)		
<200	53 (n = 159) p = 0.28	64 (n = 127) p = 0.48
≥200	47 (n = 42)	62 (n = 32)
Age (yr)		
<10	34 (n = 13)	44 (n = 10)
10–50	48 (n = 270) p = 0.90	58 (n = 216) p = 0.75
>50	52 (n = 23)	56 (n = 21)
Donor sex		
M	43 (n = 201) p = 0.16	54 (n = 159) p = 0.45
F	56 (n = 105)	64 (n = 88)
Vasopressor support		
No	39 (n = 63) p = 0.12	56 (n = 45) p = 0.45
Yes	49 (n = 243)	58 (n = 202)

TS, technically successful; UW, University of Wisconsin.

Minimizing the degree of HLA-DR as well as HLA-A, B mismatching had a favorable effect on graft survival (Table 1). No significance was seen, however, with regard to donor serum amylase, age, sex, or whether the donor was or was not on vasopressor support.

The univariate analysis of recipient factors is shown in Table 2. Factors that had a significant influence on the outcome in both the analysis of all cases as well as that of only TS cases included recipient category, method of duct management, immunosuppressive maintenance regimen, use of anti–T cell antibodies, type of graft, and era transplanted. Pancreata transplanted simultaneously with a kidney had a higher functional survival rate than those transplanted alone or after a kidney; bladder-drained grafts functioned longer than enteric or duct injected grafts; whole pancreata functioned longer than segmental grafts; grafts in patients given triple therapy functioned longer than in those given two drugs for maintenance immunosuppression; and grafts from patients given anti–T cell preparations prophylactically functioned longer than those in patients not given such treatment. There was also a significant effect of the era in which the grafts were transplanted, however; those placed in 1986 to 1990 survived longer than those placed in the earlier eras. Because all of the variables listed above were at least in part era related, whether the changes made were responsible for the improvement by era, or if the improvement by era was a nonspecific effect of our increasing experience, making the variables introduced within the various eras assume significance, is uncertain. The only recipient factors in the univariate analysis in which significant differences between values were not seen were age, sex, and whether the graft was a primary one or a retransplant.

Multivariate Analyses. The results of analyses in which only donor factors were considered in the model are shown in Table 3.

Significant factors in the analysis of all cases as well as TS cases were the degree of HLA mismatching, the pres-

TABLE 2. *Univariate Analysis of Recipient Factors That Influence Pancreas Allograft Survival: All Cadaver Donor Cases*

	% 1-yr Graft Survival	
Recipient Factors	All Cases	TS Cases
Recipient category		
PTA	42 (n = 113)} $p = 0.02$	52 (n = 92)} $p = 0.0002$
SPK	63 (n = 99)	79 (n = 79)
PAK	38 (n = 94) } $p = 0.04$	44 (n = 75)} $p = 0.00001$
Duct management		
Open	20 (n = 10) open *vs.* BD; $p = 0.02$	29 (n = 7) open *vs.* BD; $p = 0.01$
(DI)	14 (n = 35) DI *vs.* BD; $p = 0.00001$	15 (n = 33) DI *vs.* BD; $p < 0.00001$
(ED)	33 (n = 38) ED *vs.* BD; $p = 0.03$	47 (n = 25) ED *vs.* BD; $p < 0.04$
(BD)	57 (n = 221)	69 (n = 181)
Immunosuppression		
Double-drug therapy	17 (n = 50) $p < 0.00001$	20 (n = 43) $p < 0.00001$
Triple-drug therapy	53 (n = 257)	66 (n = 204)
ALG or OKT3		
No	31 (n = 128) $p < 0.00001$	41 (n = 97) $p < 0.00001$
Yes	58 (n = 179)	68 (n = 150)
Type of graft		
Whole	52 (n = 251) $p = 0.0009$	63 (n = 204) $p < 0.00001$
Segmental	27 (n = 56)	33 (n = 43)
Year of transplant		
1978–1980	23 (n = 13) 1978–1980 *vs.* 1986–1990 $p = 0.04$	28 (n = 11) 1978–1980 *vs.* 1986–1990 $p = 0.002$
1981–1985	25 (n = 69) 1981–1985 *vs.* 1986–1990 $p < 0.0001$	31 (n = 51) 1981–1985 *vs.* 1986–1990 $p < 0.0001$
1986–1990	56 (n = 225)	67 (n = 185)
Recipient age (yr)		
<45	48 (n = 290) $p = 0.18$	58 (n = 236) $p = 0.69$
≥45	25 (n = 17)	40 (n = 11)
Recipient sex		
M	47 (n = 129) $p = 0.55$	59 (n = 102) $p = 0.93$
F	47 (n = 178)	57 (n = 145)
No. of transplants		
Primary	49 (n = 235) $p = 0.68$	62 (n = 183) $p = 0.09$
Retransplant	42 (n = 72)	47 (n = 64)

TS, technically successful; PTA, pancreas transplant alone; SPK, simultaneous pancreas/kidney transplant; PAK, pancreas after kidney transplant; DI, duct injected; ED, enteric drained; BD, bladder drained.

TABLE 3. *Cox Regression Analysis of Donor Factors That Influence Pancreas Allograft Survival: All Cadaver Donor Cases*

	All Cases		TS Cases	
Factor	p	Relative Risk	p	Relative Risk
2–4 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.02	2.1	0.09	1.8
2–4 A, B mm, 0–1 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.06	1.7	NS	
0–1 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	NS		NS	
Donor glucose (mg/dL) (≥200 *vs.* <200)	0.03	1.4	0.03	1.6
1978–1980 (*vs.* 1986–1990)	NS		NS	
1981–1985 (*vs.* 1986–1990)	0.009	1.6	<0.0001	2.1
Preservation (hr) (≥30 vs <30)	0.08	3.4	NS	
Donor age (yr) (≥50 or ≤10 *vs.* other)	NS		NS	
Donor sex (M *vs.* F)	NS		NS	
Liver donor (no *vs.* yes)	NS		NS	
Vasopressor support (yes *vs.* no)	NS		NS	

TS, technically successful; mm, mismatch.

ence of hyperglycemia in the donor, and the era in which the transplant was performed.

The effect of a given degree of DR mismatch was found to depend on the level of A, B mismatch and vice versa, prompting the creation of the combined variables displayed in Tables 3, 4, 7, and 8. The relative risk associated with each of these variables is in reference to the best-matched group (0 to 1 A, B mm, 0 to 1 DR mm), which is the group that displayed the best graft survival (64% at 1 year).

Poorly matched grafts (2 to 4 A, B mm, 2 DR mm) were a risk factor in both analyses, but the level of significance in the TS cases was marginal (p = 0.09).

Preservation in excess of 30 hours was a significant risk factor in the analysis of the entire series. It did not assume importance in the analysis of TS cases, presumably because of small numbers, with most of the grafts being preserved for this length of time being classified as technical failures. Preservation times between 24 and 30 hours were associated with the best graft survival, but were confounded with era. Thus, the relative risk of 24- to 30-hour *versus* less-than-24-hour preservation could not be assessed.

The era of 1981 to 1985 remained in the model as an independent risk factor for graft loss and presumably reflects the effect of the learning curve being generated at that time. The fact that the era 1978 to 1980 was not a significant risk factor is probably due to the small number of cases (n = 13) in that early period.

A significant finding contained in Table 3 is the importance of donor hyperglycemia. A blood glucose concentration in excess of 200 mg/dL segregated as an independent risk factor in the analysis of all cases and in the analysis of TS cases. Isolated donor factors with no impact on outcome in the analysis of all and only TS cases included donor age and sex, whether or not a liver

TABLE 4. *Cox Regression Analysis of Donor and Recipient Factors That Influence Pancreas Allograft Survival: All Cadaver Cases*

	All Cases		TS Cases	
Factor	p	Relative Risk	p	Relative Risk
2–4 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.009	2.3	0.04	2.1
2–4 A, B mm, 0–1 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.03	2.0	NS	
0–1 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	NS		NS	
Donor glucose (mg/dL) (≥200 *vs.* <200)	0.04	1.4	0.02	1.7
Preservation (hr) (≥30 *vs.* <30)	0.09	3.4	NS	
Donor age (yr) (≥50 *vs.* <50)	NS		NS	
Donor sex (M *vs.* F)	NS		NS	
Liver donor (yes *vs.* no)	NS		NS	
Vasopressor support of donor (yes *vs.* no)	NS		NS	
Immunosuppression (double vs. triple drug therapy)	0.008	2.1	<0.0001	3.9
Recipient age (yr) (>45 *vs.* ≤45)	0.03	1.9	NS	
SPK (PTA *vs.* SPK)	NS		0.009	2.4
PAK (PTA *vs.* PAK)	NS		0.07	1.7
Retransplant (yes *vs.* no)	NS		0.007	1.8
Type of Graft (whole *vs.* segmental)	NS		NS	
Duct management (bladder drainage *vs.* other)	NS		NS	
ALG or OKT3 (no *vs.* yes)	NS		NS	
Recipient sex (M *vs.* F)	NS		NS	

TS, technically successful; mm, mismatch; SPK, simultaneous pancreas/kidney transplant; PTA, pancreas transplant alone; PAK, pancreas after kidney transplant.

was also procured, and whether or not the donor received vasopressor support in the perioperative period.

The results of an analysis in which both donor and recipient factors were included in the model are shown in Table 4. In this analysis, era was confounded with immunosuppressive regimen (triple-therapy *versus* double-drug regimens); therefore, both variables could not be considered simultaneously. We chose to retain the immunosuppressive regimen in the model and found that being on a double-drug regimen was the most significant risk factor in the analysis of all cases and in the analysis of only the TS cases.

The addition of recipient factors to the model did not diminish the importance of the presence of hyperglycemia in the donor. It remained an independent risk factor of similar magnitude and is in contrast to the results of an earlier analysis of our series in which donor hyperglycemia seemed to be of relatively minor importance, with its significance being outweighed by the influence of recipient variables.[20]

The degree of HLA mismatching remained an important factor, with the most poorly matched group (2 to 4 A, B mm, 2 DR mm) at significantly increased risk for graft loss. Of the remaining variables, only recipient age was of significance in the analysis of all cases. This is probably a result of diminished patient survival of older recipients. The Cox analysis of all cases rerun using patient mortality as the endpoint showed recipient age of 45 years or older to be an independent risk factor ($p = 0.02$; RR $= 4.9$; data not shown). Among the TS cases, however, recipient group was important in that recipients of a pancreas alone were 2.4 times more likely to lose their graft than were recipients of simultaneous pancreas/kidney transplants ($p = 0.009$) and 1.7 times more likely than recipients of a pancreas after a previously successful kidney transplant ($p = 0.07$).

Retransplantation was not an important prognosticator in the analysis of all cases, but in the TS group retransplant recipients were 1.8 times as likely to experience graft loss as were recipients of a primary graft ($p = 0.007$).

Of note is that the method of duct management did not factor into the model as a significant risk factor. This does not appear to be due to confounding of variables. For example, the correlation between bladder drainage and the variables found to be significant in the analysis of all TS cases was −0.06 for the degree of HLA mm (2 to 4 A, B mm, 2 DR mm), −0.22 for donor glucose, −0.31 for triple therapy, −0.17 for SPK, 0.04 for PAK, and −0.16 for retransplantation.

Analysis of Bladder-drained Cadaveric Pancreas Transplants: 1984 to 1990

To simplify the model as much as possible and retain relevance to our current transplant program, we performed both univariate and multivariate analyses of the bladder-drained pancreas transplant cases, as summarized in the following section.

Obviously duct management could not be a variable in these analyses, but neither was maintenance immunosuppression, because all recipients of bladder drained grafts were given triple therapy. Otherwise, all the factors included in the analyses of the entire series were subject to analysis in the series of bladder-drained pancreas transplants, both in the univariate and multivariate models.

Univariate Analyses. Donor hyperglycemia once again was significant. Pancreata from donors with blood glucose levels of less than 200 mg/dL had a higher graft functional survival rate than pancreata from donors with blood glucose levels higher than 200 mg/dL, whether all bladder-drained cases or only the technically successful bladder-drained cases were considered (Table 5).

Minimizing antigen mismatches at the A, B and DR loci also was associated with improved graft survival, but recipient category had less of an impact than in the analysis of the entire series (Tables 5 and 6). There was not a significant difference in functional survival rates for grafts stored in UW- *versus* the plasma-based solution. However, the functional survival rate tended to be lower for grafts stored for more than 30 hours *versus* those stored for less than 30 hours.

In contrast to the univariate analysis of the entire series, for bladder-drained cases the outcome was not better when the liver was procured, a factor that was an artifact of era in the larger analysis.

Even though this analysis spanned only from 1984 to 1990, an era effect was seen in the analysis of all bladder-drained cases (Table 6). In contrast to the univariate analysis of the entire series dating back to 1978, an adverse effect of receiving a second pancreas graft as opposed to a primary graft was evident when only the technically successful cases were considered.

Recipient category had less impact in the analysis of bladder-drained cases than in the analysis of the entire series. In fact, significance was only reached in the analysis of the TS cases. Recipients of TS simultaneous pancreas/kidney grafts fared better than recipients of a TS pancreas alone ($p = 0.01$), but not significantly better than those who received a TS pancreas after a kidney ($p = 0.15$).

Bladder-drained pancreas transplants alone did so much better than the pancreas transplants alone managed by other techniques that the differences in outcome compared with the SPK cases was much less than in the analysis of the entire series. Nevertheless, even with bladder drainage the univariate analysis showed better outcome for pancreata transplanted simultaneously with a kidney.

Multivariate Analysis. The results using the Cox model in which donor factors were analyzed for impact on outcome of bladder-drained pancreas transplants are given in Table 7. As in the analysis of donor factors alone for

TABLE 5. *Univariate Analysis of Donor Factors That Influence Pancreas Allograft Survival: Bladder-Drained Cadaver Donor Cases*

	% 1-yr Graft Survival	
Donor Factor	All Cases	TS Cases
Glucose (mg/dL)		
<200	63 (n = 97) p = 0.03	77 (n = 77) p = 0.009
≥200	50 (n = 112)	61 (n = 92)
Liver also procured		
Yes	60 (n = 112) p = 0.30	72 (n = 92) p = 0.18
No	55 (n = 106)	67 (n = 87)
Preservation time (hr)		
<24	56 (n = 188)	69 (n = 153)
24–30	68 (n = 25) p = 0.06	73 (n = 22) p = 0.59
>30	33 (n = 6)	50 (n = 4)
Preservation solution		
UW	59 (n = 104) p = 0.62	70 (n = 86) p = 0.66
Plasma based	57 (n = 113)	68 (n = 92)
AB mismatch		
0	92 (n = 14)	92 (n = 14)
1	63 (n = 29) 0 *vs.* 1; p = 0.06	76 (n = 24)
2	54 (n = 56) 0 *vs.* 2; p = 0.007	62 (n = 45) 0 *vs.* 2; p = 0.04
3	55 (n = 65) 0 *vs.* 3; p = 0.01	64 (n = 56) 0 *vs.* 3; p = 0.04
4	56 (n = 53) 0 *vs.* 4; p = 0.009	76 (n = 39)
DR mismatch		
0	63 (n = 43) 0 *vs.* 2; p = 0.08	67 (n = 39)
1	61 (n = 120)	77 (n = 95) 1 *vs.* 2; p = 0.01
2	46 (n = 57)	57 (n = 46)
Amylase (IU/L)		
<200	60 (n = 135) p = 0.18	72 (n = 111) p = 0.37
≥200	51 (n = 33)	68 (n = 25)
Age (yr)		
<10	60 (n = 5)	100 (n = 3)
10–50	58 (n = 194) p = 0.45	70 (n = 159) p = 0.06
>50	52 (n = 21)	57 (n = 19)
Sex		
M	54 (n = 136) p = 0.52	68 (n = 108) p = 0.64
F	63 (n = 84)	71 (n = 73)
Vasopressor support		
No	59 (n = 38) p = 0.83	72 (n = 32) p = 0.82
Yes	57 (n = 182)	69 (n = 149)

TS, technically successful; UW, University of Wisconsin.

the entire series, the degree of HLA mismatching had a significant impact on outcome in both the analyses of all (p = 0.003) and of TS (p = 0.006) cases, with a relative risk of 3.6 in all and 4.5 in TS cases for the most poorly matched group (2 to 4 A, B mm, 2 DR mm) *versus* the best-matched group (0 to 1 A, B mm, 0 to 1 DR mm). Perioperative glucose, however, had only a marginal impact in the analysis of donor factors alone for TS cases, in contrast to a clearly significant effect in the analysis of the entire series (Table 3). Once again, graft preservation in excess of 30 hours was associated with increased risk of graft loss when all bladder-drained cases were analyzed, but donor sex, donor age, the year in which the transplant was performed, whether or not a liver was procured, and whether or not the donor required vasopressor support in the perioperative period did not.

The addition of recipient factors to the model (Table 8) did not change the importance of the degree of HLA matching in the analysis of all bladder-drained cases. The impact of HLA matching was still measurable in the analysis of the TS cases, but it was less pronounced than when only donor factors are considered.

As in the analysis of donor and recipient factors in the entire series, the presence of donor hyperglycemia was of prognostic importance, more so in the TS cases (RR = 1.9, p = 0.04) than in the analysis of all bladder-drained grafts. Recipients of TS simultaneous pancreas/kidney transplants continued to have a higher pancreas graft survival rate than recipients of TS pancreas transplants alone. In contrast to the results in the overall series, however, recipients of a pancreas transplant alone in the bladder drainage era were not at a significantly higher relative risk of graft loss than were recipients of a pancreas after a previously successful kidney transplant, again reflecting the better results achieved in the current era in the pancreas transplant alone group. Preservation of the graft in excess of 30 hours continued to be a variable of marginal prognostic significance.

The increased risk associated with retransplantation was apparent in the analysis of all bladder-drained cases and

TABLE 6. *Univariate Analysis of Recipient Factors That Influence Pancreas Allograft Survival: Bladder-Drained Cadaver Donor Cases*

	% 1-Year Graft Survival	
Recipient Factor	All Cases	TS Cases
Recipient Category		
PTA	52 (n = 71)	59 (n = 62)} p = 0.01
SPK	63 (n = 99) p = 0.60	79 (n = 79)
PAK	56 (n = 50)	67 (n = 39)} p = 0.15
ALG or OKT3		
No	58 (n = 44) p = 0.21	81 (n = 33) p = 0.87
Yes	58 (n = 177)	68 (n = 148)
Type of graft		
Whole	57 (n = 213) p = 0.55	69 (n = 175) p = 0.58
Segmental	50 (n = 8)	67 (n = 6)
Year of transplant		
1984–1987	50 (n = 60) p = 0.03	66 (n = 44) p = 0.24
1988–1990	60 (n = 161)	70 (n = 137)
Recipient age (yr)		
<45	58 (n = 208) p = 0.21	69 (n = 173) p = 0.99
≥45	37 (n = 13)	63 (n = 8)
Sex		
M	55 (n = 94) p = 0.28	68 (n = 75) p = 0.60
F	59 (n = 127)	70 (n = 106)
No. of transplants		
Primary	60 (n = 170) p = 0.13	73 (n = 138) p = 0.03
Retransplant	48 (n = 51)	57 (n = 43)

TS, technically successful; PTA, pancreas transplant alone; SPK, simultaneous pancreas/kidney transplant; PAK, pancreas after kidney transplant.

was more pronounced in the analysis of the TS bladder-drained cases than it was in the analysis of the entire series of cadaver grafts (Table 4). To better gauge the magnitude of the adverse impact of retransplantation on graft survival, we used the Cox model to construct estimated survival functions for recipients of bladder-drained grafts, stratified according to whether the graft was primary or a retransplant. This analysis was stratified also by recipient category and by the degree of HLA matching, with an average histocompatibility match (2 to 4 A, B mm, 0 to

TABLE 7. *Cox Regression Analysis of Donor Factors That Influence Pancreas Allograft Survival: Bladder-drained Cadaver Cases*

	All Cases		TS Cases	
Factor	p	Relative Risk	p	Relative Risk
2–4 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.003	3.6	0.006	4.5
2.4 A, B mm, 0–1 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.01	2.9	0.07	2.7
0–1 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	NS		NS	
Donor/Glucose (mg/dL) (≥200 *vs.* <200)	NS		0.09	1.6
Year of transplant (1984–1987 *vs.* 1988–1990)	NS		NS	
Preservation (hr) (≥30 *vs.* <30)	0.04	4.6	NS	
Donor age (yr) ≥50 *vs.* <50	NS		NS	
Donor sex (M *vs.* F)	NS		NS	
Liver donor (yes *vs.* no)	NS		NS	
Vasopressor support of donor (yes *vs.* no)	NS		NS	

TS, technically successful; mm, mismatch.

TABLE 8. *Cox Regression Analysis of Donor and Recipient Factors That Influence Pancreas Allograft Survival: Bladder-drained Cases*

	All Cases		TS Cases	
Factor	p	Relative Risk	p	Relative Risk
2–4 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.008	3.2	0.04	3.3
2–4 A, B mm, 0–1 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	0.01	2.9	NS	
0–1 A, B mm, 2 DR mm (*vs.* 0–1 A, B mm, 0–1 DR mm)	NS		NS	
Donor glucose (mg/dL) (≥200 *vs.* <200)	0.07	1.5	0.04	1.9
Preservation (hr) (≥30 *vs.* <30)	0.07	4.0	NS	
Donor age (yr) (≥50 *vs.* <50)	NS		0.07	2.2
Donor sex (M *vs.* F)	NS		NS	
Liver donor (yes *vs.* no)	NS		NS	
Vasopressor support of donor (yes *vs.* no)	NS		NS	
Recipient age (yr) (>45 *vs.* ≤45)	NS		NS	
SPK (PTA *vs.* SPK)	NS		0.007	2.7
PAK (PTA *vs.* PAK)	NS		NS	
Retransplant (yes *vs.* no)	0.04	1.7	0.003	2.6
Type of graft (whole *vs.* segmental)	NS		NS	
ALG or OKT3 (no *vs.* yes)	NS		NS	
Recipient sex (M *vs.* F)	NS		NS	

TS, technically successful; mm, mismatch; SPK, simultaneous pancreas/kidney transplant; PTA, pancreas transplant alone; PAK, pancreas after kidney transplant.

1 DR mm) being compared with an excellent tissue match (0 to 1 A, B mm, 0 to 1 DR mm). The values of the other variables were held constant and were selected to represent the average clinical situation (*i.e.*, preservation time not more than 24 hours, donor age between 10 and 50 years, recipient age not more than 45 years, liver also procured, anti–T-cell agents used for induction, and no vasopressors used to support the donor in the perioperative period).

The results of retransplantation varied, depending on the recipient category and the degree of HLA matching, with the estimated 1-year functional survival rate varying from a low of 38% in the average matched PAK group to 80% in the well-matched SPK group (Fig. 1). An important finding was that the estimated functional survival of retransplants dramatically improved when well-matched grafts were used. For example, 1-year survival rate in the PAK retransplant group (the category most commonly associated with retransplantation) increases from 38% when the degree of HLA match is average (Fig. 1C) to 72% when an organ with an excellent histocompatibility match is available (Fig. 1D).

Analysis for Risk Factors Associated With Technical Failure

Because the factors responsible for technical failures are probably different than the factors associated with graft loss due to rejection, a separate logistic regression analysis was performed, looking for risk factors associated with technical failure.

No factors were significantly associated with technical failure in the analysis of the entire series. Both era and hours of preservation, however, were significant risk factors when only the bladder-drained cases (n = 221) were considered ($p < 0.05$). Transplants performed during the years 1984 to 1987 when the bladder-drainage technique was being developed were more likely to fail because of technical reasons (27%) than transplants performed in 1988 to 1990 (15%). Similarly, long preservation times were associated with technical failure, with 33% of grafts preserved for longer than 30 hours being classified as technical failures, in contrast to 18% of grafts preserved for less than 30 hours.

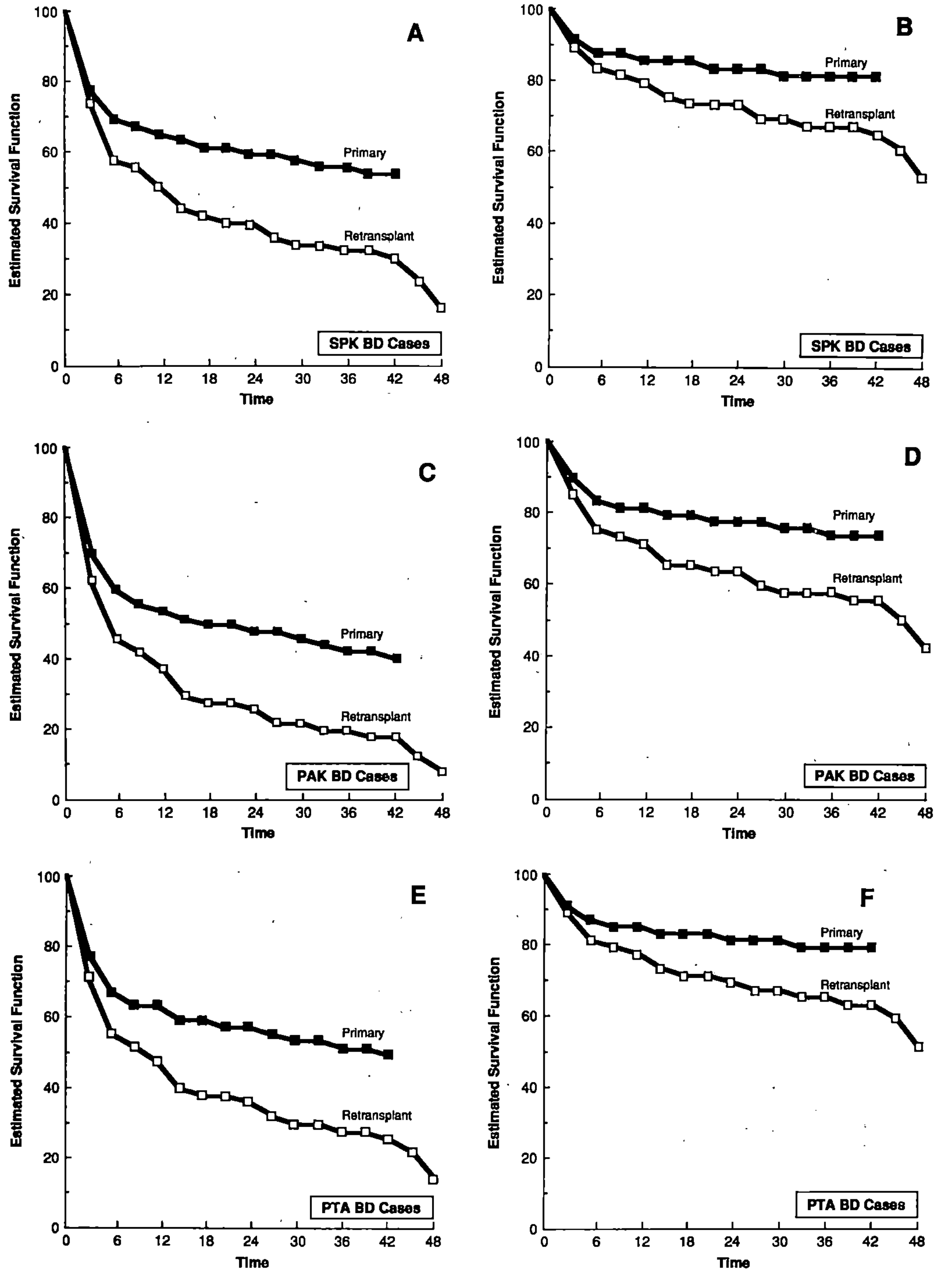

FIG. 1. Estimated pancreas allograft functional survival for primary grafts and retransplants in (A) bladder-drained simultaneous pancreas/kidney transplant (SPK) patients with 2–4 A, B and 0–1 DR HLA mismatch; (B) bladder-drained SPK patients with 0–1 A, B and 0–1 DR HLA mismatch; (C) bladder-drained pancreas after kidney transplant (PAK) patients with 2–4 A, B and 0–1 DR HLA mismatch; (D) bladder-drained PAK patients with 0–1 A, B and 0–1 DR HLA mismatch; (E) bladder-drained pancreas transplant alone (PTA) patients with 2–4 A, B and 0–1 DR HLA mismatch; and (F) bladder-drained PTA patients with 0–1 A, B and 0–1 DR HLA mismatch. See text for values of other variables used in construction of the curves.

Discussion

Failure of a pancreatic allograft can be attributed to either immunologic or nonimmunologic (*i.e.*, technical) causes. Mechanisms of nonimmunologic graft loss include thrombosis, infection, and pancreatitis. Technical failures account for approximately 15% to 25% of graft losses,[1,12–14] and the factors that are responsible for a graft becoming a technical loss may not be the same as the factors contributing to loss by rejection. Therefore, in addition to analyzing our entire experience with cadaver donor allografts, we also separately analyzed the technically successful grafts. We also looked at our technical failures in an attempt to identify risk factors associated with them. In an earlier report,[11] we noted that on univariate analysis donor hyperglycemia was associated with significantly decreased long-term graft function. This association was also found in the current univariate analysis. Nine other variables were also found to be significant on univariate analysis, however, illustrating the need for a multivariate approach.

The most significant risk factor identified in the analysis of the entire series was the regimen used for immunosuppression. Patients receiving triple therapy experienced better allograft survival than patients placed on a double-drug regimen, with triple therapy being an especially powerful prognosticator of graft survival in the technically successful group.

The degree of HLA mismatching also was found to be of considerable prognostic importance. In the univariate analysis, both the degree of A, B mismatch and the degree of DR mismatch were significant variables. Those grafts that were mismatched for a larger number of A, B or DR antigens functioned for a shorter period than more well-matched grafts did. The adverse impact of poor HLA matching was apparent also in the multivariate analysis, where the effect of the degree of A, B mismatch could not be separated from the effect of the degree of DR mismatch (*i.e.,* there is an interaction between the degree of A, B mm and the degree of DR mm such that the effect of a given level of A, B mm depends on the degree of DR mm present and *vice versa*).

For the entire series, the 1-year graft survival ranged from 64% for the best matched group (0 to 1 A, B mm, 0 to 1 DR mm) to 38% for the most poorly matched group (2 to 4 A, B mm, 2 DR mm). The adverse influence of poor HLA matching was seen in every multivariate analysis (*i.e.,* the analysis of all cadaver cases as well as the analysis of only the bladder-drained cases and their technically successful subgroups).

The results of retransplantation of other organs are generally not as good as the results of primary transplants,[21–23] and this is at least partly explained by the fact that the cohort of patients coming to retransplantation have shown themselves as a group to be high responders immunologically. In a previous univariate analysis of our data, the results of pancreas retransplantation were significantly worse when performed simultaneously with a kidney, but not when performed after a kidney or alone.[24] In the Cox analysis reported here, however, overall retransplantation has a negative impact on outcome.

Although recipients of retransplants face an increased risk of graft loss, our success rate, 48% at 1 year with bladder drainage, is high enough to justify continuing our policy of offering patients the opportunity to receive another pancreas if the first fails. Furthermore, the results of retransplantation are significantly improved by using donors well matched for HLA type (Fig. 1).

In the technically successful groups, pancreas grafts placed simultaneously with a kidney were more likely to survive than those placed after a kidney or those transplanted alone in nonuremic, non-kidney transplant recipients. This can again be explained on immunologic grounds, with the SPK recipients faring better because of an ability to diagnose rejection earlier by monitoring serum creatinine. Thus, in spite of the emphasis others have placed on the importance of nonimunologic factors in determining outcome,[2] in our analysis immunologically related variables were preeminent, the only exception being donor glucose.

The presence of hyperglycemia (blood glucose $\geq$ 200 mg/dL) in the donor was an independent risk factor associated with decreased graft survival (Tables 4 and 8). This may reflect a decreased functional reserve of the β cell mass in these donors. The observation that donor hyperglycemia was a more significant risk factor in the analysis of only the technically successful cases supports this notion, because losses in this group are secondary to rejection. Presumably, pancreata from donors who remained relatively normoglycemic (blood glucose <200 mg/dL) during the physiologically stressful period surrounding organ donation have a greater functional β cell mass reserve, which enables them to weather repeated bouts of acute allograft rejection more readily than the pancreata procured from hyperglycemic donors. It is noteworthy that in the analysis of only the bladder-drained cases, this same relationship of donor hyperglycemia and increased risk of graft loss was observed. All of the bladder-drained transplants have been performed since 1984, and the results in this group reflect the effect of the many changes we incorporated into the management of pancreas transplant recipients during our initial learning curve. Despite this, the presence of hyperglycemia in the donor remains as an independent risk factor.

This finding raises the question as to whether donors with a blood glucose concentration in excess of 200 mg/dL, who are otherwise acceptable, should be used. To enable us to better answer this question, we used the Cox model to construct estimated survival functions for recipients of bladder-drained grafts stratified by the level of donor glucose. The values of the other variables were held constant and were selected to represent the average clinical situation, just as in the analysis of retransplantation described above. The degree of HLA matching was assumed to be 2 to 4 A, B mm, 0 to 1 DR mm. Forty-six per cent of grafts from hyperglycemic donors were estimated to be functioning at 1 year, compared with 60% of grafts from donors with blood glucose concentrations less than 200 mg/dL (data not shown). The analysis was extended, with estimated survival functions according to donor blood glucose being constructed for recipients of primary bladder-drained grafts and for recipients of retransplant bladder-drained grafts. The magnitude of the penalty paid for using a hyperglycemic donor was similar in the two groups (data not shown). Because recipient category was an independent risk factor in the analysis of TS bladder-drained cases (Table 8), we reasoned that perhaps the magnitude of the penalty for using a hyperglycemic donor would be less in the SPK group. We therefore further stratified the analysis to include recipient category; as can be seen in Figure 2, the decreased functional graft survival rate observed in recipients of grafts from hyperglycemic donors was similar in every category, with the magnitude of the penalty at 1 year varying only between 14% and 18%.

If the poorer results associated with donor hyperglycemia are related to a smaller reserve of functional β cell mass, any measures that reduce the incidence or severity of rejection episodes would tend to minimize the penalty associated with using such donors. The other alternative is not to use hyperglycemic donors, but this strategy would greatly reduce the donor pool (by more than 50% in our experience; see Tables 1 and 5).

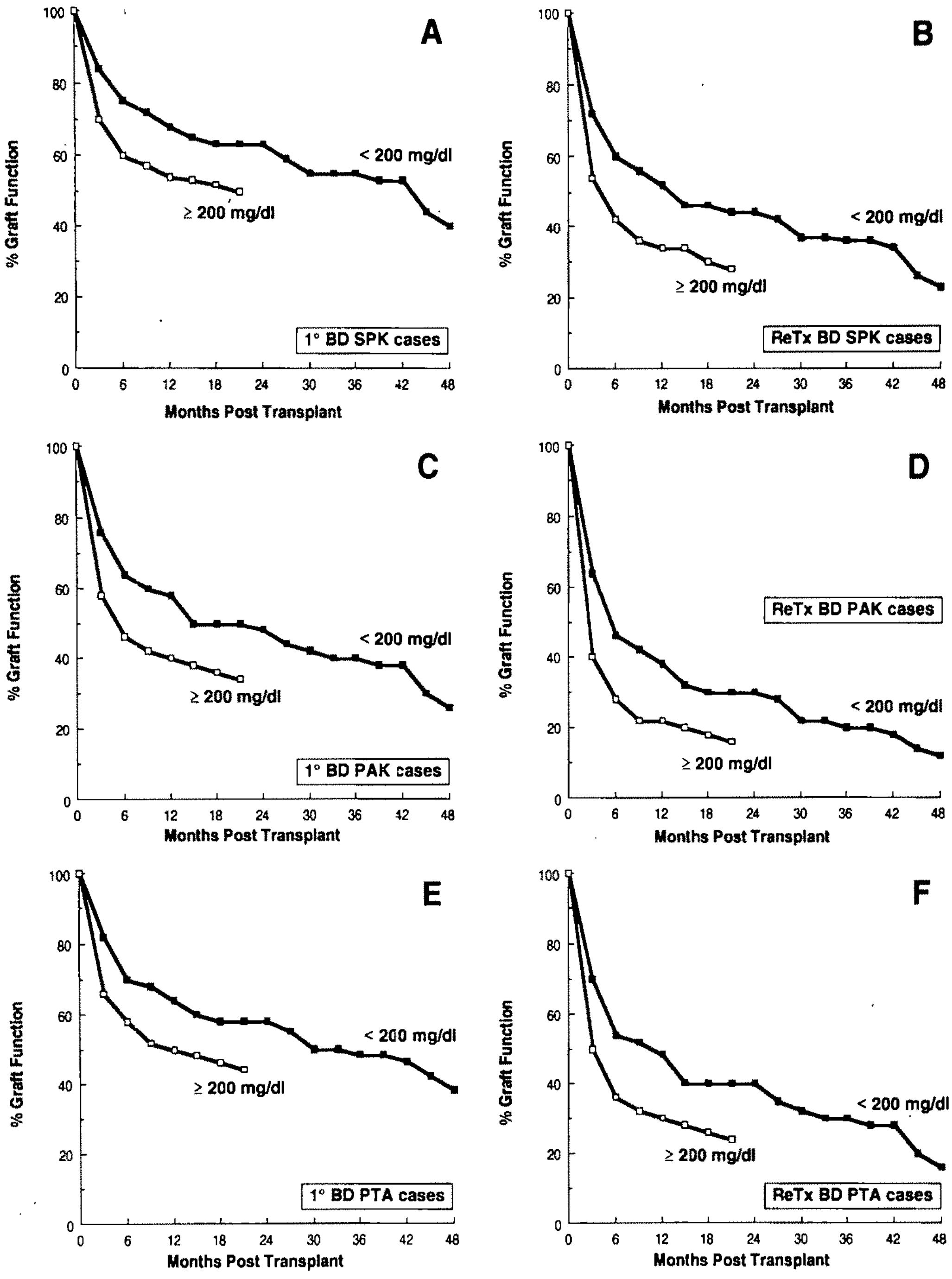

FIG. 2. Estimated pancreas allograft functional survival according to the presence or absence of donor hyperglycemia in (A) primary bladder-drained simultaneous pancreas/kidney transplant (SPK) patients, (B) retransplant bladder-drained SPK patients, (C) primary bladder-drained pancreas after kidney transplant (PAK) patients, (D) retransplant bladder-drained PAK transplant, (E) primary bladder-drained pancreas transplant alone (PTA) patients, and (F) retransplant bladder-drained PTA patients. Degree of HLA mismatching assumed to be 2–4 A, B, 0–1 DR. See text for values of other variables used in construction of the curves.

We changed the model to investigate the effect of donor hyperglycemia on the functional survival of well-matched grafts (0 to 1 A, B mm, 0 to 1 DR mm) and found the degree of the penalty to be somewhat less, with 1-year functional survival of 76% and 84% of grafts from hyperglycemic donors and from donors with blood glucose concentrations less than 200 mg/dL, respectively (data not shown). When the analysis was stratified by primary grafts *versus* retransplants as well as by recipient category, the grafts from well-matched hyperglycemic donors consistently exhibited a shorter functional survival rate than grafts from well-matched normoglycemic donors (Fig. 3). The results were dramatically better, however, than the projections obtained using an average donor/recipient HLA match, particularly for retransplants (Fig. 2). For example, recipients of a primary simultaneous pancreas/kidney transplant (currently the most common clinical situation in which pancreas transplantation is performed

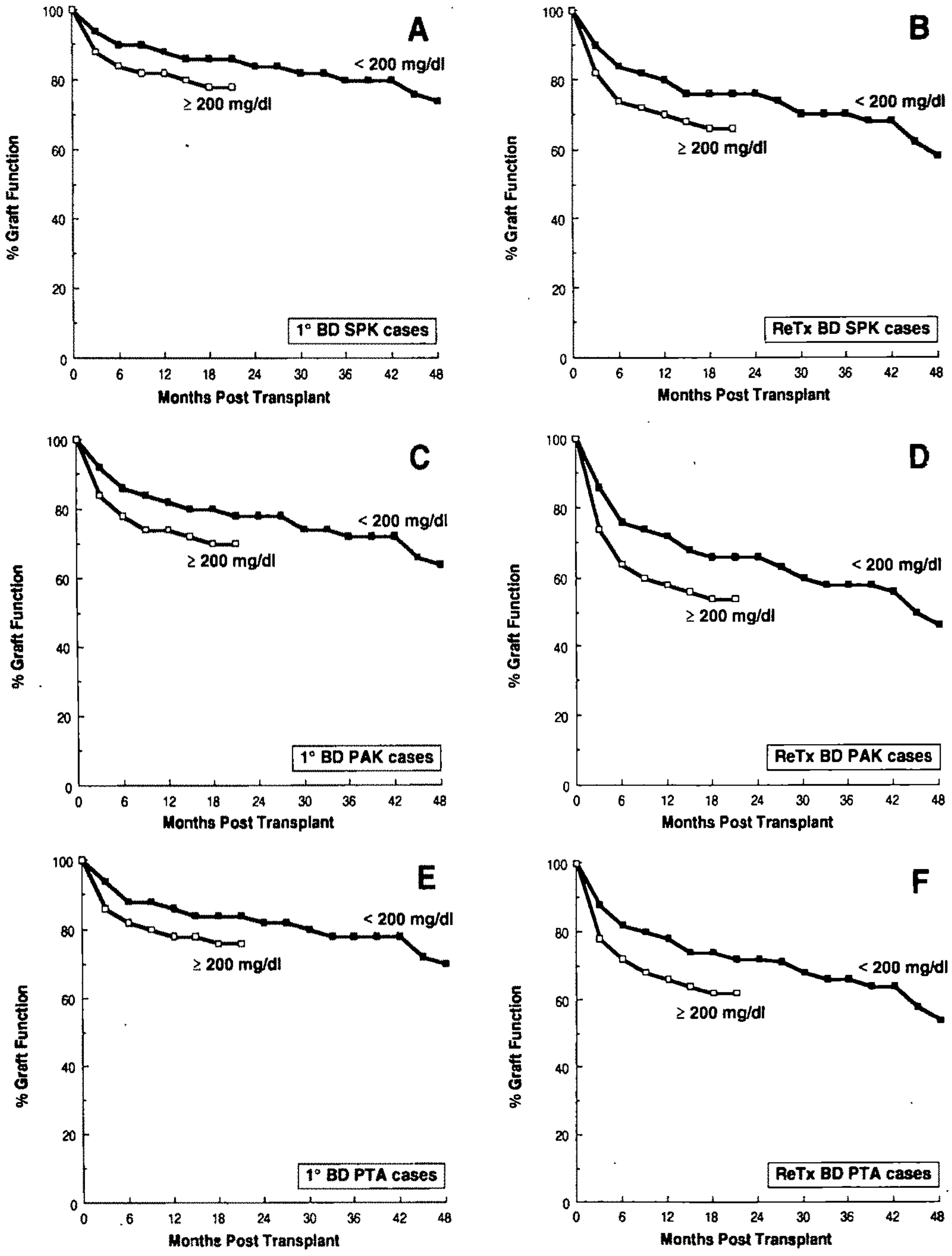

FIG. 3. Estimated pancreas allograft functional survival according to the presence or absence of donor hyperglycemia in (A) primary bladder-drained simultaneous pancreas/kidney transplant (SPK) patients, (B) retransplant bladder-drained SPK patients, (C) primary bladder-drained pancreas after kidney transplant (PAK) patients, (D) retransplant bladder-drained PAK patients, (E) primary bladder-drained pancreas transplant alone (PTA) patients, and (F) retransplant bladder-drained PTA patients. Degree of HLA mismatching assumed to be 0–1 A, B, 0–1 DR. See text for values of other variables used in construction of the curves.

worldwide) are estimated to exhibit an 88% graft functional survival rate at 1 year if the graft is procured from a well-matched, normoglycemic donor. If the donor is hyperglycemic, the estimated 1-year functional survival rate is 82% (Fig. 3A). The corresponding figures for a graft from a donor exhibiting an average degree of HLA matching with the recipient are 68% and 54% (Fig. 2A).

Thus, it appears that the level of the blood glucose concentration is an important factor to consider when evaluating the suitability of a potential donor. None of the hyperglycemic donors used in our series had a diagnosis of diabetes by history, and we assume the hyperglycemia to be a reflection of the known effects of central nervous system trauma on raising blood sugar level,[25] as well as the effect of steroids and high-volume infusion of glucose-containing solutions. Presumably, donors who remain normoglycemic under these physiologically stressful conditions have more β cell reserve than those who do not, but because the degree of insulin resistance is probably independent of β cell mass, the degree of hyperglycemia will not have a perfect correlation. If donor hyperglycemia is not simply a sign of heightened resistance to insulin utilization peripherally, but is also a marker for the presence of a relatively smaller functional β cell mass reserve, one would predict that until the problem of rejection is overcome (*i.e.*, tolerance is achieved), the functional survival rate for grafts from hyperglycemic donors will remain inferior to grafts from relatively normoglycemic donors. Although rejection episodes are a commonplace occurrence with our current protocols of immunosuppressive management, functional graft survival is improved by good HLA matching (Tables 4, 8, and Fig. 3). The fact that the penalty paid, in terms of functional graft survival, for using a pancreas from a hyperglycemic donor is minimized by using well-matched grafts may be explained by fewer and less severe rejection episodes observed in that situation.

Rather than not use hyperglycemic donors, our results argue that grafts from such donors should be placed in well-matched recipients. This can be achieved by having a large recipient pool, and argues for sharing between centers. This argument is further bolstered by the results of retransplantation of well-matched organs and by the fact that there is no adverse effect of preservation times up to 30 hours on graft survival rates.

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Preoperative Indications for Extended Pancreatectomy for Locally Advanced Pancreas Cancer Involving the Portal Vein

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This retrospective study attempted to determine the indications for extended pancreatectomy for locally advanced carcinoma of the pancreas, in terms of postoperative prognosis. An extended pancreatectomy with portal vein or superior mesenteric vein (PV/SMV) resection and regional lymphadenectomy was performed in 35 of 50 consecutive cancers that extended into the retroperitoneal spaces and involved the PV or SMV. Among the many background factors in the 35 resected specimens, the degree of PV/SMV invasion by the cancer was most closely associated with prognosis, despite resection of all involved PV/SMV. This factor generally correlated with the preoperative findings on the portal phase of superior mesenteric arteriograph. In 17 selected patients in whom PV/SMV invasion had been angiographically both semicircular or less and 1.2 cm (1.4 cm on the film) or less in length, the 3-year survival rate was 59%. This survival rate was significantly higher than the 29% 3-year survival rate in all 35 patients ($p < 0.05$). Conversely, among the 18 patients in whom invasion was angiographically either beyond semicircular or more than 1.2 cm (1.4 cm on the film) in length, there were no 1.5-year survivors, and this result was even worse than that of 15 nonresectable cases. Based on postoperative survival, the degrees of PV/SMV invasion on preoperative angiography (narrowing pattern and length) are good indicators for aggressive pancreatectomy for locally advanced pancreatic cancer.

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THE INCIDENCE OF ductal cell carcinoma of the pancreas has risen recently in many countries. Although surgical resection is the only curative modality for this cancer, the fact remains that most patients are diagnosed in advanced stages. At the time of surgical exploration, even though distant metastases are not detectable, we frequently observe that the pancreatic tumor extends directly into the retroperitoneal spaces and involves the superior mesenteric vein (SMV) or portal vein (PV). Such a locally advanced pancreatic cancer, stage III in the UICC (International Union Against Cancer) classification,[1] has been generally treated by radiotherapy or chemotherapy.

Aggressive *en bloc* pancreatic resection including the PV or SMV (PV/SMV) has almost been abandoned,[2,3] because of the higher mortality rate, low curability rate, and lower quality of life.

With the recent advances in postoperative care, however, both mortality and morbidity rates have been remarkably decreased after pancreatectomy.[4,5] Second, the development of a bypass catheter and an extracorporeal pump have made it easier and safer to concomitantly resect the PV/SMV.[6] Third, our previous report[7] showed that postoperative survival was significantly improved, especially when lymphatic and connective tissue resection (R2-dissection) was added to the traditional pancreatectomy. Therefore, we have attempted since 1984 to resect more advanced cancer directly extending into the retroperitoneal spaces and PV/SMV, by adding the R2-procedure plus PV/SMV-resection. This type of pancreatectomy is almost similar to Fortner's regional pancreatectomy.[8] Although he failed to improve overall survival (median survival period was 13 months with a 3-year survival rate of 3%), we must reconsider that most of his patients were in highly advanced stages. Therefore, it is suspected that he might have experienced a greater number of long-term survivors if he had applied his procedure to less advanced cancer of the pancreas. Additionally, with more strict indications, we can avoid useless laparotomy or pancreatectomy in patients whose survival period would not be thereby prolonged. Thus, the present study was conducted to detect reliable indicators of surgical resection for locally advanced cancer of the pancreas. We also analyzed the predictability of preoperative examinations.

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Patients and Methods

During the period from 1984 to 1989, surgical laparotomy was performed in 50 consecutive patients with locally advanced adenocarcinoma of the pancreatic head and body at The Center for Adult Diseases, Osaka, Japan. Although none had hepatic metastasis or peritoneal seeding, the tumors extended directly into the retroperitoneal spaces and involved the PV/SMV in all patients. With a curative intent, 35 patients (70%) received an extended pancreatectomy with *en bloc* resection of a 3.1 ± 0.9 cm length of PV/SMV (Table 1). Additionally, peripancreatic connective tissue, including both regional and juxtaregional lymph nodes, were clearly dissected (R2) in all 35 patients. Thirty-five pancreatectomies consisted of 18 Whipple procedures (Child's method with a slight modification), 15 total pancreatectomies, and 2 (subtotal) caudal pancreatectomies. The appropriate range of the PV/SMV resection was determined with the aid of intraoperative histocytology. Bypass catheter[6] (Anthron Catheter, Tore Co. Ltd. Tokyo, Japan) combined with extracorporeal pump was used for four cases whose PV/SMV invasions were 3.5 cm or more in length. The PV/SMV reconstruction was performed by end-to-end anastomosis: PV/SMV in 16 patients, PV-graft (femoral vein)-SMV in 3 patients, and SMV-SMV in 16 patients. In four patients, superior mesenteric artery (SMA; three patients) or common hepatic artery (one patient) was resected because of identification of a small amount of cancer invasion. These arteries were reconstructed by interposing a graft obtained from the saphenous vein. The tumor invasion was still more extensive in another 15 patients, invading the root of the transverse mesocolon or the root of mesojejunum. Curative resection of the tumor was therefore abandoned, and gastrojejunostomy or choledochojejunostomy were performed.

TABLE 1. *Outcome of 35 Surgical Resections for Locally Advanced Adenocarcinoma of the Pancreas*

Procedure	No. of Patients	No. of Deaths After Surgery
Pancreatectomy		
Total	15	2
Whipple procedure (Child's method)	18	
Caudal	2	
Major vessels resected		
SMV	15	
SMV + SMA	1	
SMV + PV	15	1
SMV + PV + SMA	3	1
SMV + PV + CHA	1	

Regional and juxtaregional lymph nodes were cleared in all 35 patients. SMV, superior mesenteric vein; SMA, superior mesenteric artery; PV, portal vein; CHA, common hepatic artery.

The surgically resected specimens were studied histologically to determine the tumor size (maximum diameter), nodal involvement, and histologic type. In the present study, the PV/SMV were judged as positive for cancer invasion even when cancer cells were limited to the tunica adventitia. The length of PV/SMV invasion was measured, and the width was also classified into two grades on the basis of whether cancer invasion was beyond the semicircle of the PV/SMV or not. Before surgery, all 50 patients had undergone both celiac arteriography and superior mesenteric angiography, using a modified Seldinger technique.[9] To better delineate the SMV and PV, 20 μg prostaglandin E1 (Ono Pharmacologic Co. Ltd., Tokyo, Japan) was injected through the catheter into the SMA just before filming. All angiographs were examined to detect evidence of encasement or narrowing in the major vessels adjacent to the pancreas. The patterns of PV and SMV narrowing were categorized into five types. The length of PV/SMV invasion was determined on the angiographs, and was divided by 1.2 (magnification rate).

The cumulative survival rate was shown by life-table method. Statistical analyses performed using nonpaired t test or chi square test. P values less than 0.05 were considered to be statistically significant.

Results

Thirty-five patients received pancreatectomy, PV/SMV resection, and peripancreatic connective tissue resection, including the regional lymph nodes, for locally advanced carcinoma of the pancreas. Two died of postoperative complications within 30 days, and three are alive without disease recurrence between 1 and to 3 years after surgery. Among the remaining 30 patients, 23 patients (77%) died of cancer recurrence within 3 years after surgery (Group A) (mean survival period, 9 ± 5 months; range, 2 to 21 months). Seven patients (23%) survived 3 years or more (Group B), and five of these were disease free at 3 years.

Table 2 compares both the patients and their pancreatic carcinomas in groups A and B. There are no significant differences in age, sex, location of the tumor (head or body), or tumor size. The histologic types of cancer were classified into two types: papillary/well-differentiated adenocarcinoma and moderately/poorly differentiated adenocarcinoma. The latter type represented 57% in group A, which was not significantly higher than the 43% in group B. Histologically proven nodal involvement in the regional or juxtaregional areas was seen in 28 (93%) of 30 patients. The incidence of nodal involvement did not differ significantly between the two groups. There were four patients (17%) whose major arteries were involved by cancer (SMA = 3, common hepatic artery = 1) in group A, but this incidence was not significantly higher than 0% in group B. It was histologically confirmed that

TABLE 2. *Background Factors in Association With 3-Year Survival*

Factor	Patient Survival Period <3 yr (23 patients)	 >3 yr (7 patients)	p
Age (yr)	61 ± 7	63 ± 4	NS*
Sex	16/7	5/2	NS†
Tumor location (head/body)	17/6	5/2	NS†
Tumor size (cm)	3.6 ± 0.8	3.3 ± 1.4	NS*
Histologic type			
Pap + Well	10 (43%)	4 (57%)	
Mod + Poor	13 (57%)	3 (43%)	NS†
Regional lymph node metastasis			
Positive/negative	21/2	7/0	NS†
Major artery invasion‡	4 (17%)	0 (0%)	NS†
PV/SMV invasion			
Semicircular or less	12 (52%)	7 (100%)	<0.05†
Beyond semicircular	11 (48%)	0 (0%)	
Maximum length (cm)	2.6 ± 1.0	1.6 ± 0.4	<0.05*
Range	1.0–5.4	0.9–2.0	

* Nonpaired t test.

† Chi square test.

‡ Common hepatic artery, 3; superior mesenteric artery, 1.

Pap: papillary adenocarcinoma; Well: well-differentiated adenocarcinoma; Mod: moderately differentiated adenocarcinoma; Poor: poorly differentiated adenocarcinoma; PV, portal vein; SMV, superior mesenteric vein.

all 30 of the PV/SMV were involved by cancer, but the degree of cancer invasion differed significantly between the two groups. Among 23 PV/SMV invasions of group A, 12 (52%) were semicircular or less, and 11 (48%) were beyond semicircular. Conversely, the PV/SMV invasion was semicircular or less in all the patients (100%) of group B ($p < 0.05$, chi square test). Likewise, the length of PV/SMV invasion was 2.6 ± 1.1 cm (1.0 to 5.4 cm) and 1.6 ± 0.4 cm (0.9 to 2.0 cm), respectively ($p < 0.05$ in nonpaired t test).

To know whether PV/SMV invasion can be predicted by preoperative angiography, a retrospective analysis was made on the portal phase of SMA-angiography. The PV/SMV was clearly delineated in all 50 patients, and the findings were classified into the following five types (Fig. 1): (I) normal, (II) smooth shift without narrowing, (III) unilateral narrowing (Fig. 2A), (IV) bilateral narrowing (Fig. 2B), and (V) bilateral narrowing and the presence of collateral veins. Table 3 compares the patterns of PV/SMV invasion between histology and angiography in the 35 resectable patients. Among the 35 cases showing invasion, angiography resulted in 14 (40%) underestimations (as shown by a: type I and II in both groups, and type III in the group with bilateral narrowing). Likewise, there were 19 correct diagnoses (54%; shown by b) and two overestimations (6%; shown by c). Among the 22 PV/SMV invasions that were semicircular or less, however, 20 (91%) exhibited types I, II, or III. This incidence was significantly higher than the 15% (two cases) in 13 cases whose invasions were beyond the semicircle of PV/SMV ($p < 0.05$). Fifteen nonresectable cases consisted of eight cases of type IV and seven cases of type V.

Figure 3 compares the length of PV/SMV invasion determined by the histopathology of the resected specimen with those diagnosed by preoperative angiography. In this figure, the angiographic lengths of PV/SMV invasion were expressed as 0 cm for 13 cases with type I or II patterns, shown by open circles. Even excluding these 13 cases, the true length of PV/SMV invasion was longer than the angiographic length in all but one case. There was a parallel relationship, however, between the two types of measurement ($y = 0.68 \times -0.17$, $r = 0.766$, $p < 0.01$). Among the 17 cases whose PV/SMV invasions were 2 cm or less (area delineated by dotted line), 1.2 cm of invasion was the longest based on angiographic diagnosis. Although the true lengths of cancer invasion were not known for the 15 nonresectable cases, angiography showed invasion of 1.5 cm or more in length. There were 17 patients in whom PV/SMV invasion was angiographically 1.2 cm or less in length and who were type I, II, or III.

Figure 4A shows the cumulative survival rates in the 35 overall resectable cases and 15 nonresectable cases.

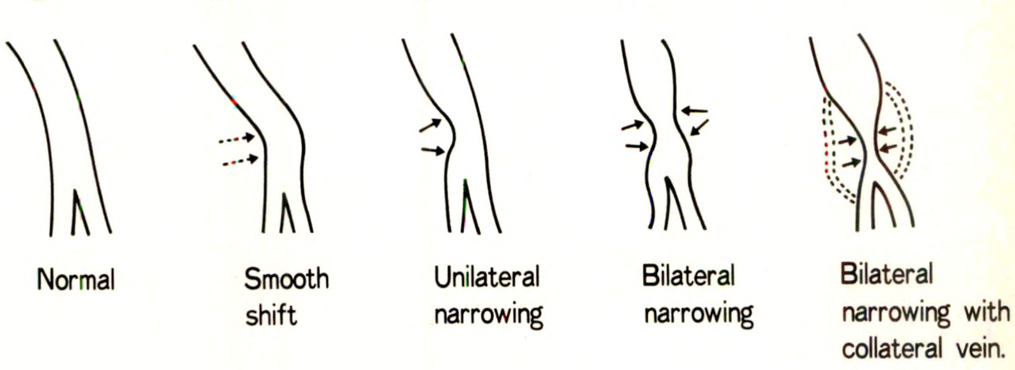

FIG. 1. Angiographic typing of PV/SMV invasion.

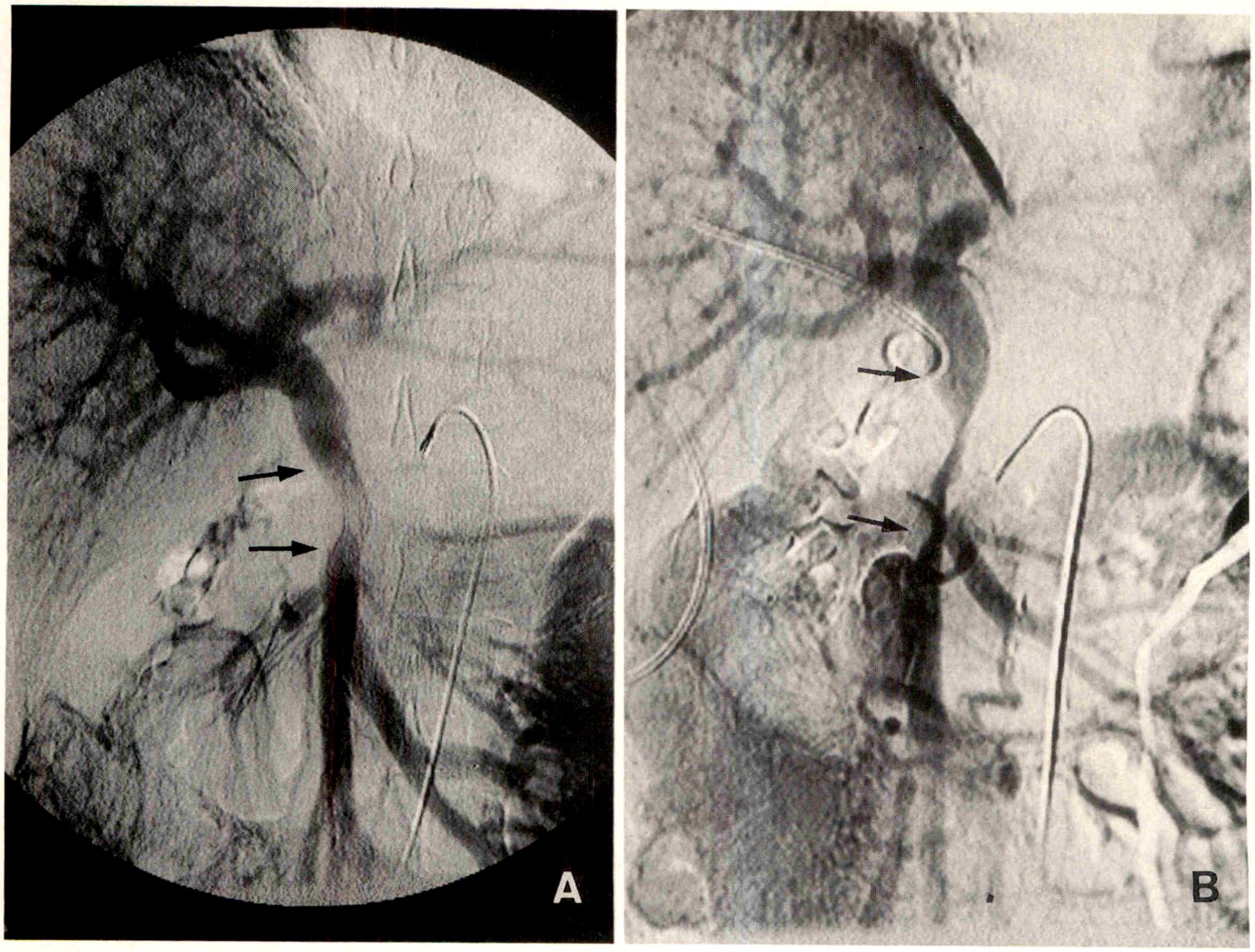

FIG. 2. Portal phase of SMA angiography, (A) types III and (B) type IV narrowing. The length of the narrowed portion (between arrows) is determined on the angiographic film and divided by 1.2 (magnification rate).

The 3-year survival rate was 29% and 0%, respectively ($p < 0.05$ at 2 and 3 years). Figure 4B shows the cumulative survival rates of two subgroups: 17 patients in whom PV/SMV invasion had been angiographically diagnosed as type I, II, or III, and 1.2 cm or less in length; and 18 patients in whom invasion had been diagnosed as type IV or V, or more than 1.2 cm in length. In the former subgroup, the 3-year survival rate was 59%. This figure was significantly higher than the 29% in all resectable cases ($p < 0.05$). Conversely, there were no 1.5-year survivors in the latter subgroup. The survival rate was generally lower than that of the 15 nonresected patients (Fig. 4A) in whom curative resection was abandoned because the retroperitoneal invasion was extensive.

TABLE 3. *Comparison of the Patterns of PV/SMV Invasion Between Histology and Angiography*

PV/SMV Invasion in Resected Specimen	Portal Phase of SMA angiography				
	I	II	III	IV	V
Semicircle or less (n = 22)	5* (23%)	7* (32%)	8† (36%)	2‡ (9%)	0
Beyond semicircle (n = 13)	1* (8%)	0	1* (8%)	6† (46%)	5‡ (38%)

The incidence of types I–III (or types IV–V) narrowing differs significantly between unilateral and bilateral invasion groups ($p < 0.01$) (chi square test).

* Underdiagnosis, 14 cases (40%).

† Correct diagnosis, 19 cases (54%).

‡ Overdiagnosis, 2 cases (6%).

PV, portal vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery.

Discussion

The present study was limited to locally advanced pancreatic cancers invading both the retroperitoneal spaces and PV/SMV. As shown in Table 1, almost all patients had regional or juxtaregional lymph node metastasis. In reviewing previous reports,[10–12] such an advanced cancer commonly has been considered not suitable for the surgical resection. There have been few patients to date, however, whose survival periods have been prolonged

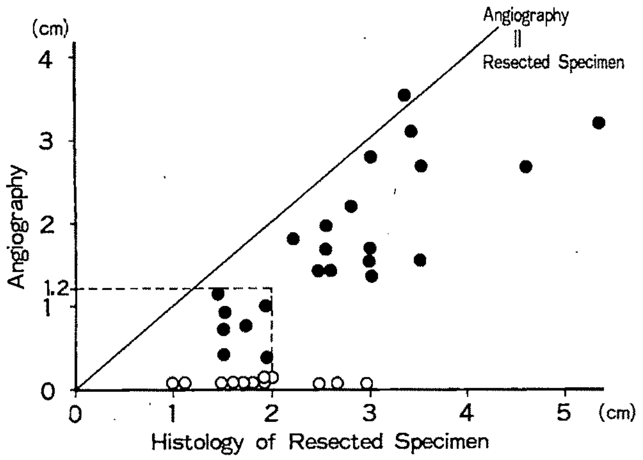

FIG. 3. A comparison of the length of PV/SMV invasion between histology and angiography. Open circles show cases in which any narrowing was angiographically observed (types I and II). Excluding the cases with type I and II narrowing, a parallel relationship is observed between the two measurements ($y = 0.68$, $x = 0.17$, $r = 0.766$, $p < 0.05$). Dotted lines show that all invasions of 2 cm or less in length were angiographically diagnosed as narrowings of 1.2 cm or less in length.

more than 3 years by chemotherapy or radiation therapy.[10-12] This agrees with our result, in which the 2-year survival rate was 0% in 15 nonresectable patients (Fig. 4A). Additionally, many previous reports have shown that pancreatic cancer was likely to recur and be fatal within 2 or 3 years after surgical resection.[7,13,14] It can be expected from this that patients who have survived the first 3 postoperative years have a high potential for cancer-free survival from that time on. This is why 3-year survival was used as a tentative parameter of operative indications in the following discussion.

During surgical resection of pancreatic cancer, nodal involvement has been considered one of the limiting factors in patient survival. In 1982, Cohen et al.[15] showed that long-term survival could not be expected for any patients with nodal involvement. Our recent report,[7] however, clarified that long-term survival was not hopeless, even in patients with nodal involvement, when lymphatic and connective tissue resection (R2-procedure) also was performed. Considering that all of our seven 3-year survivors had lymphatic metastasis in the regional or juxtaregional nodes, most might not have survived 3 years if the R2-procedure had been omitted from our operative procedure. Therefore, this kind of lymphadenectomy seems to be indispensable when surgical resection is determined for locally advanced pancreatic cancer.

In place of nodal involvement, our study has clarified that the degree (length and width) of PV/SMV invasion was more predictive of patient prognosis, despite resection of all involved PV/SMV. For this reason, the space between the SMV or PV and the posterior confines of the pancreas may be anatomically characterized as the weakest barrier against cancer spread into the mesenteric tissues, which include many lymphatic channels and nerve fibers.[16] Likewise, cancer cells within the PV/SMV wall may easily spread hematologically and result in hepatic metastasis. The more widely the cancer invades the PV/SMV, the more frequently and distant from the surgical margin cancer implantation might occur microscopically.

Suzuki et al.[17,18] reported that long-term survival was not observed in pancreatic cancer patients whose arteriographs suggested cancer invasion in the arteries adjacent to the pancreas. Despite the fact that PV/SMV involvement is more common than arterial involvement in pancreatic cancer,[19] there has been no previous report investigating patient survival in association with PV/SMV invasion on angiography. For the first time, the present report has clarified that postsurgical prognosis is very poor in patients in whom angiography showed bilateral narrowing (type IV or V) or more than a 1.2 cm (1.4 cm on the film) length of narrowing in the PV/SMV. Considering that their survival rates were worse than those of the nonresectable patients, we should have abandoned aggressive pancreatectomy in these patients. This also seems to be

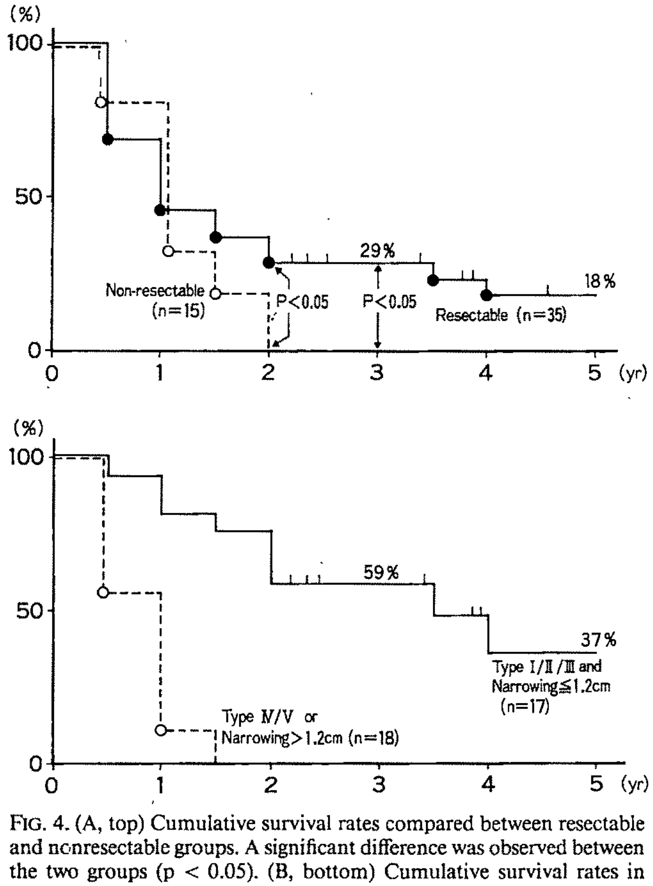

FIG. 4. (A, top) Cumulative survival rates compared between resectable and nonresectable groups. A significant difference was observed between the two groups ($p < 0.05$). (B, bottom) Cumulative survival rates in association with angiographic findings in the resectable group. In the subgroup with both type I–III narrowing and narrowing of 1.2 cm or less in length, the 3-year survival rate was 59%. This figure is significantly higher than the 29% found in all 35 patients (A). In the subgroup with either type IV–V narrowing or narrowing greater than 1.2 cm in length, the survival rate is still worse than that of the 15 nonresectable patients (A).

supported from the viewpoint of cost-performance and quality of postoperative life. Conversely, a far better prognosis can be expected for patients in whom PV/SMV narrowing is angiographically absent, unilateral, and 1.2 cm (1.4 cm on the film) or less in length. If we had selected the above-mentioned criteria as indications for aggressive operation, approximately a 60% 3-year survival rate would have been estimated by extended pancreatectomy (Fig. 4B). This result is better than many previous reports[4,7,20,21] where 3-year survival rate ranged from 20% to 45%, even in less advanced carcinoma of the pancreas.

The portal phase of SMA angiography was likely to underestimate the true invasion of the PV/SMV (Fig. 3 and Table 3). This discrepancy might be explained by the fact that the internal diameter of the PV/SMV would be unaffected during the period when cancer invasion is limited to the tunica adventitia. Therefore, we should always prepare to perform PV/SMV resection and their reconstruction when pancreatectomy is performed for carcinoma of the pancreatic head and body. This is especially emphasized when no obvious change is observed angiographically in the PV/SMV.

Finally, our angiographic classification is very simple and does not require percutaneous transhepatic portography[22] to clearly delineate any branching veins. Using this classification of the traditional SMA-angiography, we can hope that useless laparotomy or pancreatectomy can be avoided without losing any chance for cure.

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Postoperative Electromyographic Profile in Human Jejunum

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The postoperative electromyographic profile of the proximal jejunum and its evolution during recovery from surgery were defined in fasted humans after cholecystectomy. An intraluminal probe supporting four groups of bipolar electrodes was transnasally inserted at the end of surgery to allow continuous recording of jejunal electrical activity over 4 consecutive days. Electromyographic activity was characterized by an early reappearance of phase 3 of migrating myoelectric complexes (MMC) lasting 5.2 ± 0.6 minutes and occurring at 38.1 ± 3.1-minute intervals at day 1 after surgery. During the 4 days after surgery, there was an increased duration of MMC, mainly consisting of phase 2 occurrence with an increased duration and lengthening of the MMC cycle. The amplitude of spikes during phase 3 increased. During the postoperative period, characterized by an inversion of the circadian rhythm, the velocity of propagation was higher ($p < 0.05$) between 18:00 and 06:00 (4.0 ± 0.5 cm/minute) than between 06:00 and 18:00 (3.1 ± 0.3 cm/minute). In contrast, the duration of phase 2 was lower during nighttime (18:00 to 06:00) than during daytime. The authors conclude that during the early (1 to 2 days) period after cholecystectomy, the jejunal electromyographic activity is limited to phase 3 activity, but that a normal fasted pattern is recovered after 4 days. A progressive reorganization and coordination of the intestinal tract may account for this delay.

POSTOPERATIVE ILEUS IS characterized by temporarily impaired gastrointestinal motility causing discomfort, increased morbidity rate, and prolonged hospitalization. After operation, the slowed transit of solids is subsequent to the suppression of the migrating burst of action potentials and contractions,[1] which are observed throughout the gut during fasting in humans.[2-5]

The interdigestive electromyographic (EMG) activity of the small bowel of humans displays a cyclic pattern, characterized by the interdigestive migrating myoelectric complex (MMC). This complex consists of three successive phases[4]: a quiescent phase 1 with slow waves only; a phase 2 with increasing action potential activity superimposed on some slow waves; and a phase 3 of maximal activity with action potentials on every slow wave, lasting several minutes. A phase 4 of rapid return to phase 1 is sometimes described. Correspondingly, the cyclic motor activity of the small intestine has little or no contractile activity in phase 1, intermittent and irregular contractions during phase 2, and a maximal rate of contraction during phase 3.[4,6,7]

Inhibition of intestinal EMG activity is considered to be transient in gastric antrum and of short duration in the small bowel, suggesting that the postoperative ileus is only a colonic problem.[8] The radiographic characterization of early motility of the gastrointestinal tract after surgery was recognized many years ago.[9] Several observations report that MMC are present in the upper intestine during the early postoperative period,[10-12] whereas others indicate a late recovery after surgery.[13,14] All these studies focused on the early restoration of MMC in the upper intestine, or on the characterization of this activity at a given time after surgery, but only two of them[11,12] described the evolution of intestinal EMG activity during the first days of surgical recovery. The main result of the previous report[11] was the early reappearance of phase 3 activity in the small bowel, in addition to a recovery of normal activity after gas expulsion, which was marked by an EMG disorganization.

The aim of this study was to verify this pattern of recovery but also to go into the temporal evolution of the phenomenon in the course of the first 4 postoperative days. In particular we wanted to reexamine the question of the EMG disorganization before the normal transit recovery. Therefore, the present study was designed to pro-

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vide more information on the different patterns of the jejunal electromyographic activity after abdominal surgery and on the continuous evolution of this pattern after a single type of surgery, cholecystectomy, using an intraluminal probe introduced by nasal route.

Patients and Methods

Patients

The protocol was approved by the ethical committee Claude Bernard University Review Board for Human Studies). Between 1989 and 1990, the EMG activity of the upper intestine was investigated in 10 patients aged 50 to 80 years, seven women and three men, after abdominal surgery consisting of cholecystectomy. All patients underwent surgery at approximately the same time of day. Recordings were performed immediately after abdominal closure and continuously over 4 days after surgery. Anesthesia was realized with phenoperidine (R1406, Janssen LeBrun, Paris, France) as morphinomimetic, at a dose of 2 to 6 mg according to the duration of operation, but always administered more than 30 minutes before the end of operation. Postoperative treatment consisted of rehydration, antibiotics, and preventive heparin therapy. Opiate analgesics were excluded in all cases. All patients had normal recovery from abdominal surgery. Informed consent was obtained from each patient, and the probe was withdrawn for patients presenting any sign of discomfort or gastric pain. None of them resorted to this possibility.

Recordings

Continuous recordings of the first 60 cm of the upper intestine were obtained by an intraluminal probe derived from that of Fleckenstein[6] and the one previously described by Pouyet et al.[11] The intraluminal probe consisted of a sterilizable polyvinyl tube (150 cm in length and 8 mm in diameter) supporting four groups of two electrodes placed at 5-mm intervals, the groups being 7 cm apart, and one ground electrode. The first group was located 7 cm from the tip. Each electrode (0.11 mm in diameter) consisted of a ring of nickel-chrome wire (80% to 20%; Johnston Matthey Metals Ltd, London, UK) fixed around the probe. The sensor consisted of three separated tubes: a large one, ending at the top of the sensor for parenteral nutrition; a smaller one, ending at 100 cm of the distal end for gastric emptying; and the smallest, in the lumen of which the wires leading from the electrodes to the recorder were inserted to exit at the distal end.

The probe was introduced transnasally at the end of surgery before abdominal closure, with manual guidance to pass over the pylorus, and positioned so that the gastric aperture was at the level of the pyloric antrum and the four groups of electrodes were in the jejunum. During postoperative recovery, the position of the probe was ascertained by x-ray radiography, showing the probe with a radiopaque signal at the top of the probe and the ground electrode located 25 cm from the top. The probe was localized in relation to its position from the ligament of Treitz.

The free ends of the wires were connected to an eight-channel polygraph (Reega VIII, Alvar, Paris, France), and bipolar recordings were performed with a short time constant (0.01 second) at a paper speed of 1.2 cm/minute, or at a larger time constant (0.8 second) and paper speed (2.4 cm/second) for slow wave recording.

The parameters studied were the duration of MMC, the respective durations of each phase of MMC, and the duration, amplitude, and migrating velocity of phase 3. The MMC was divided into three sequential phases: phase 1 was characterized by the absence of activity or the presence of some occasional spike potentials; the criteria of phase 2 was the appearance of irregular activity that increases in intensity throughout the phase, until the phase 3 occurrence. Phase 1 duration was obtained by subtracting the duration of phase 2 from the total duration of MMC. Phase 4 was not considered.

We did not measure the amplitude of every spike burst because it would have represented a considerable number of measurements and it was difficult to distinguish every spike burst of one phase 3 episode at the paper speed used. The mean amplitude of the spike bursts was obtained by a planimetric method, allowing the measurement of the envelope area around each phase 3 complex, and thereby the mean amplitude of phase 3. This enabled a consistent decrease of the number of measurements.

Statistical Analysis

Results are expressed as mean ± standard error of the mean (SEM). The values were pooled and averaged in each patient per periods of 6 hours per day through the 4 days of the study. The means ± SEM values were calculated from the mean values of each parameter on each period of time per subject. Statistical significance of parameter evolution through surgical recovery was assessed by one-way analysis of variance followed by paired Student's t test.

Results

Clinical Observations

All patients had normal postsurgical recovery as evidenced by the absence of abnormal clinical signs and the presence of gas expulsion between the second and third day after surgery. The mean hospitalization duration was 7 days.

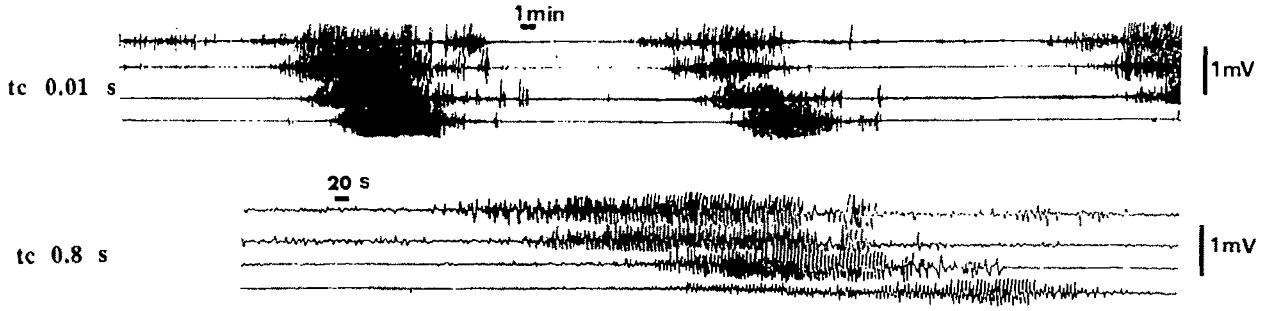

FIG. 1. Electromyographic recording of human jejunum with a short time constant (0.01 sec) showing only spiking activity and with a high time constant (0.8 sec) displaying slow waves and spiking activity obtained during the first day after cholecystectomy. The samples shown here are different events on the same subject.

Jejunal EMG Profile After Surgery

Electromyographic recordings 3 hours after surgery demonstrated the presence of phase 3 lasting 5.2 ± 0.6 minutes and occurring at 38.1 ± 3.1-minute intervals during the first 6 hours of recording in jejunum, as shown in Figure 1. These "ectopic" complexes were characterized by the absence of phase 2, however, and were composed only of the quiescent phase 1 and repetitive bursts of spikes similar to the phase of regular spiking activity or phase 3 of the MMC. These peculiar complexes are called postoperative migrating myoelectric complexes. During the quiescent period, the slow waves appeared regularly at a rhythm of 12.2 ± 0.2 per minute.

Jejunal EMG Recovery After Surgery

The duration of postoperative MMC increased progressively (F = 2.1; $p < 0.05$) from 38.1 ± 3.1 minutes at day 1 (just after operation) to 67.8 ± 10.2 minutes at day 4 of surgical recovery (Fig. 2). Concomitantly, the duration of phase 2 progressively increased from 2.1 ± 0.9 minutes (day 1, 12:00 to 18:00) to 42.2 ± 6.8 min (F = 11.7; $p < 0.001$), until a normal pattern and characteristics of MMC were reached (phase 1: 31%; phase 2: 62%; phase 3: 7%) corresponding to those reported in the literature.[4] A significant variation (F = 2.2; $p < 0.01$) was observed in phase 3 duration through the 4 days of recovery, mainly because of a small increased duration at day 2 (Fig. 2, Table 1). In parallel, the mean amplitude of spike bursts during phase 3 progressively increased from 0.39 ± 0.01 mV at day 1 to 0.52 ± 0.01 mV at day 4 (F = 2.6; $p < 0.01$) (Table 1). The velocity of phase 3 (Fig. 3) decreased progressively from day 1 to day 4 of recovery, but not regularly (F = 4.4; $p < 0.001$). Indeed, a circadian variation of the migrating velocity was observed: during day 2, the velocity of propagation was lower (3.1 ± 0.2 *versus* 4.0 ± 0.3 cm/minutes; $p < 0.01$) during daytime (06:00 to 18:00) than during nighttime (18:00 to 06:00). No significant nyctohemeral variation was detected at day 3, whereas lower velocity ($p < 0.05$) was recorded during nighttime (18:00 to 06:00) at day 4 (3.0 ± 0.2 *versus* 3.6 ± 0.2 cm/minute, $p < 0.01$) than during daytime (Fig. 4). A nyctohemeral variation also appeared in the duration of phase 2, as reported in Figure 3, with maximal values during day time, but not in duration of phase 1, phase 2, and MMC, nor in amplitude of phases 2 and 3.

In contrast, the rhythm of slow waves appeared unchanged over the 4 days of surgical recovery, as could be observed from partial recordings at longer time constants performed at different days after surgery. Further, because the tube did not incorporate suction to keep the electrodes applied to the mucosa, it could have induced an intermittent identification of slow waves. Therefore, the evolution of slow waves was not monitored during the time course of surgical recovery.

Discussion

Our study confirms that MMC are present in humans in early surgical recovery, thereby confirming earlier observations.[10–12] It also describes for the first time the pattern of total recovery as well as the nyctohemeral variations up to the fourth day in fasted state. Other studies have reported the first postoperative occurrence of MMC between the second and fifth days after surgery[13] or between the sixth and ninth days.[14] In contrast, Dauchel et al.[15] did not find MMC after cholecystectomy, but only disorganized slow waves during the first 36 hours. In a previous study, we showed that the common feature of intestinal electrical recovery[11] may be divided into three phases: a first one of early reappearance of postoperative myoelectric complexes lasting about 90 hours, a very short second phase of EMG disorganization just after gas expulsion, and then, a third phase of normalized MMC. The present study confirms the first part of this pattern, but failed to indicate an EMG disorganization.

The profile of recovery after cholecystectomy was characterized by an early electric spiking activity of the small bowel, which resulted at jejunal level, in a higher frequency and lower duration of isolated and ectopic phase 3 com-

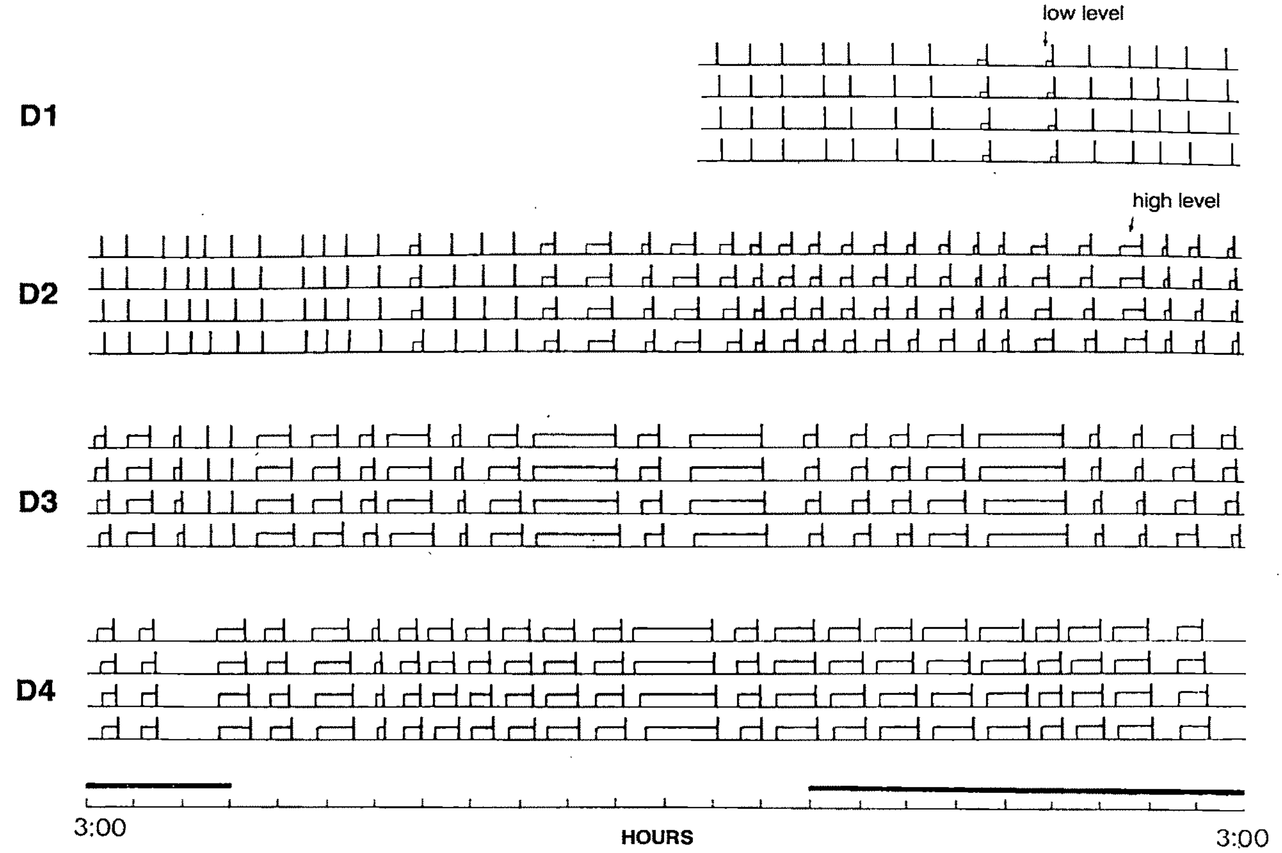

FIG. 2. Four-day postoperative electromyographic profile of the jejunum in one patient 3 hours after cholecystectomy. Diagrammatic representation of the electromyogram for the four groups of electrodes at, respectively, 10, 17, 24, and 31 cm from the ligament of Treitz. Black columns show the phases of regular spiking activity (phase 3). Open areas show irregular spiking activity (phase 2). Note that phase 3 is present at the beginning of the first recording session. ▬, night time.

pared with values of MMC in normal subjects reported elsewhere.[2,3,5,7] The values we report here in human jejunum are in agreement with those previously reported[11] during the first 24 postoperative hours. In the present study, the higher velocity of propagation (3.9 ± 0.2 cm/minute) compared with the previously referred works may be explained by a more proximal position of the jejunal electrodes, because the migration velocity gradually decreases along the small bowel.[2,4,5] These results also may be compared with values reported in human duodenum,[13] either for total duration of complexes (41.9 ± 3.4 minutes), or of phase 2 (5.7 ± 1.0 minutes) and phase 3 (4.7 ± 0.3 minutes) between the second and fifth postoperative days.[13] They are also in agreement with some early postoperative duodenal values,[10] but at variance with others.[12] Indeed, in the latter study also performed on cholecystectomized patients but with serosal electrodes implanted in the duodenum, the frequency of occurrence of phase 3 was very low at day 1 after surgery, and increased thereafter,[12] contrary to the results of the present study.

After surgery, the early appearance and permanence of electrical activity limited to phase 3 episodes suggest that they play an important role in maintaining a functional small intestine. This early high frequency of phase 3 is probably not related to the presence of the sensor because no significant mechanical effect of intraluminal probe was

TABLE 1. *Postoperative Characteristics of Phase 3 of Migrating Myoelectric Complexes in 10 Patients at Different Days (D) After Cholecystectomy*

Amplitude (mV)				Duration (min)			
D1	D2	D3	D4	D1	D2	D3	D4
0.39 ± 0.01	0.49 ± 0.03	0.54 ± 0.01	0.52 ± 0.01	5.2 ± 0.6	5.9 ± 0.5	5.7 ± 0.5	5.4 ± 0.4

Mean ± SEM.

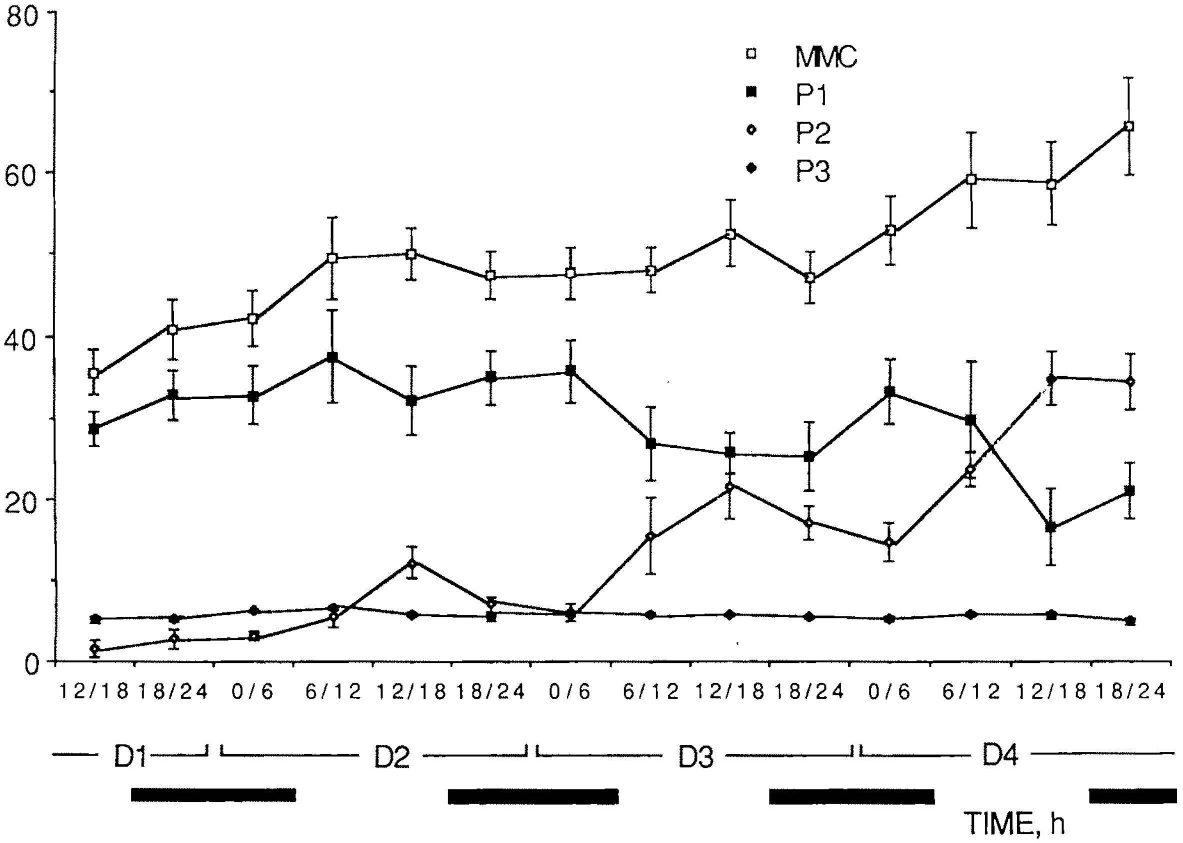

FIG. 3. Changes in the duration (min) of postoperative migrating myoelectric complexes and of its phases over the 4 days (D1–D4) after cholecystectomy (mean ± SEM, n = 10 patients). Each day is divided into periods of 6 hours. ▬, night time.

found in comparison with muscular implanted electrodes.[16] According to their role of "housekeeper,"[17] phase 3 episodes ensure the homeostasis of the bacterial content of the small bowel in preventing bacterial overgrowth.[7,18] Therefore, they might be useful in repelling the colonic flora after surgery. The frequent occurrence of phase 3 persisted until the recovery of phase 2, whereas the propagation velocity decreased. The reappearance of phase 2 episodes induced an increased duration of postoperative complexes. In contrast, no significant increase in duration of the complexes was found between the second and fifth postoperative days by Stoddard et al.,[13] but these authors

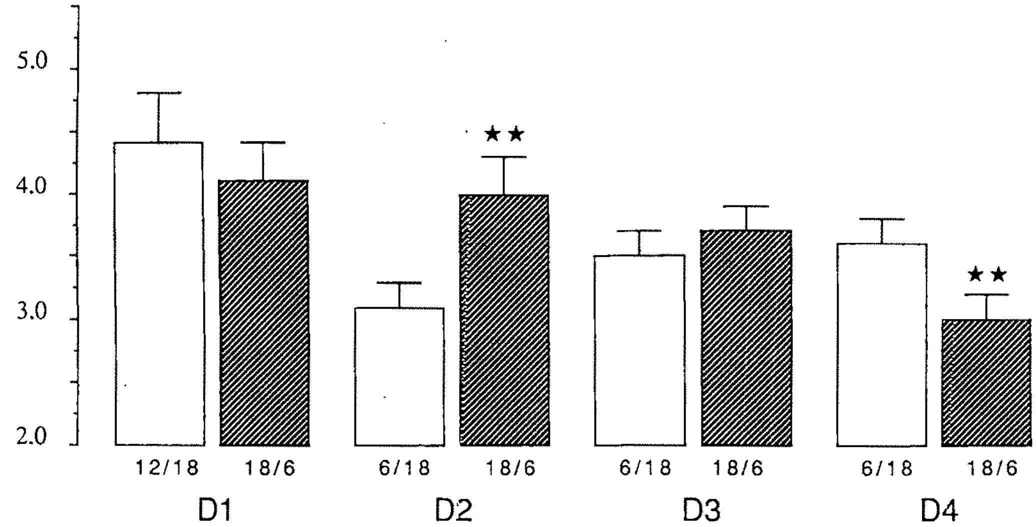

FIG. 4. Postoperative nyctohemeral variations in the propagation velocity (cm/min) of phase 3 over 4 days (D1–D4) after cholecystectomy (mean ± SEM, n = 10 patients). Each day is divided into periods of 6 hours. **p < 0.01 *vs.* the preceding period.

did not continuously monitor the EMG activity during this period.

It is generally accepted that MMCs originate in the gastroduodenal area and mainly (50% to 60%) in the duodenum.[4,5] In patients, the removal of the gastric antrum after the Billroth II procedure is associated with a striking increase in the frequency of the phase 3 activity fronts recorded by a manometric probe,[19] as observed either after truncal vagotomy with splanchnicectomy[20] and after complete denervation of an autotransplanted intestinal loop.[21] Therefore, it may be assumed that the gastric antrum continuously reduces the intestine's own frequency of MMC occurrence.[22] After surgery, duodenal motor activity usually returns well before gastric contractions appear.[9,10] In this case, the absence of inhibitory influences related to gastric motor activity on the duodenum may explain the observed increased number of jejunal phase 3 activity fronts. It has been shown that the delay in the return of gastric motility after abdominal surgery was the consequence of disordered electrical control activity of the stomach.[23] The progressive (2 to 3 days) reappearance of normal MMC of the jejunum would seem to be related to an improvement of gastroduodenal coordination, but further experimental investigation is required to confirm this hypothesis.

Conversely, our results show a circadian variation in the durations of phase 2, and of migration velocity in the postoperative period. Some circadian variations in MMC propagation velocity have been reported in upper intestine of healthy humans,[24] with a higher propagation velocity during daytime than during the night. In the present study, phase 3 propagated at a higher velocity between 18 and 6 hours than between 6 and 18 hours during the second day, whereas normal circadian variations appeared on the fourth postoperative day. This suggests that the disruption of the circadian modulation system, induced by surgery or anesthesia, takes at least 3 days to return to normal. It is generally accepted that the enteric nervous system is able to program and integrate enteric motor activity,[4,25] and it was suggested that the variation in propagation of the MMC reflected the speed of transmission within the enteric nervous system.[24] In cholecystectomy, the integrity of the small bowel is preserved. Therefore, the disruption of the enteric nervous system could be attributed rather to the effect of anesthesia, or laparotomy, because it was shown in dogs and sheep that laparotomy induced a complete inhibition of electrical spiking activity[26] and thus would be liable to disorganize such a system. Laparotomy rather than anesthesia may be the important variable. The observed enteric oscillation, however, also could be a consequence of circadian modulation by the central nervous system, as suggested by the nocturnal reduction of phase 2 reported here. This phenomenon is to be compared with the known reduction of the irregular contractions of phase II during sleep,[27,28] suggesting that the sleep–waking pattern can modulate enteric activity. It has to be noted that in humans there is a similar period for both MMC and sleep cycles.[29]

The question arises whether a profound disruption of the sleep–waking pattern after surgery might account for the observed postoperative changes, as well the absence of phase 2s as the inversion of the nyctohemeral cycle. Indeed, during the first day after operation, the patients were rather somnolent most of the time (as we could judge), but they did not appear to be continuously asleep. Thereafter, the 18:00 to 06:00. period included most of the sleep hours. Therefore, the reorganization of the enteric activity seemed to parallel the recovery of a normal sleep–waking pattern. If a reduction of the number of contractions in phase II was found during sleep,[27,28] however, no complete disappearance was observed. Thus, this could not be, in our opinion, the simple explanation of the phenomenon. Further, in the absence of electroencephalographic activity recordings in the present study, the nyctohemeral repartition of sleep, as well as the quality of the sleep episodes and the connection with EMG activity, can hardly be appreciated and remain to be determined.

The present results failed to indicate a marked EMG disorganization at the time of gas expulsion and just before the normal transit recovery, as was previously found.[11] The return to normality was principally achieved by a reorganization of the nyctohemeral variations in the phase 3 propagation velocity at the fourth day after surgery, at a time when the disorganized EMG was reported. This difference with the previous report could result from the different populations studied. The abdominal surgery of the present subjects consisted only of cholecystectomy, whereas in the previous study, only 2 of 20 subjects were cholecystectomized. This suggests that the postoperative recovery pattern may depend on the type of surgery, but further studies are required to clarify this point.

In conclusion, the recovery of jejunal electrical activity after surgery described in this study emphasizes the early presence of phase 3, but the persistence of motor alteration until the fourth day. This delay, accounted for by a progressive reorganization and coordination of the intestinal tract, should be taken into account in postsurgical care.

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Improvement in Survival From Typhoid Ileal Perforation

Results of 221 Operative Cases

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Typhoid ileal perforation remains a frequently fatal illness in the developing world. The purpose of a retrospective review of 195 cases was to ascertain prognostic indices and therapeutic options influencing outcome. The overall mortality rate of 31% was worsened by extremes of age ($p < 0.025$), generalized peritonitis ($p < 0.025$), lower white blood cell count ($p < 0.05$), increased number of perforations ($p < 0.005$), and postoperative enterocutaneous fistula ($p < 0.005$). Double-layer closure of the perforation lowered the mortality rate compared with single-layer closure ($p < 0.01$). Broader-spectrum antibiotics, in the form of chloramphenicol with gentamycin, metronidazole, or both, reduced the mortality rate compared with chloramphenicol alone ($p < 0.05$). Based on these findings, a prospective series was initiated in which all patients were treated with two-layer closure and chloramphenicol, gentamycin, and metronidazole. The mortality rate of 8% for the 26 patients treated in this manner confirmed the improved survival with these treatment modalities. Improved survival from typhoid perforation is possible with simple, low-cost measures.

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ALTHOUGH SALMONELLA TYPHI infection causing typhoid fever has become rare in the United States and other developed nations in recent decades, it continues to be a major health problem throughout most of the developing world. A severe complication and a frequent cause for death from typhoid is perforation of ileal ulcerations. The reported mortality rates of 20% to 60%[1-11] for this complication are especially high in view of the young age of many of the patients.

Typhoid ileal perforation has traditionally been treated with surgical plication and with chloramphenicol. The mortality rate could be improved with the use of better supportive care, including parenteral nutrition and invasive monitoring. Such measures are beyond the reach of many hospitals in the developing world, however. The purpose of the present study was to examine the management of this complication of typhoid fever and to determine which variables could be manipulated to improve survival. First, a retrospective review was undertaken to ascertain prognostic indices and results of different treatment regimens. Then, a prospective series was initiated in which therapy was based on the findings of the review.

Methods

Patients undergoing surgery for typhoid ileal perforation at the Holy Family Hospital, Berekum, Ghana form the basis for this study. This is a 160-bed facility serving a predominantly rural population of 200,000. The hospital has basic operative facilities, but supportive care such as mechanical ventilation, parenteral nutrition, and invasive monitoring are unavailable. Plain radiographs and determinations of hemoglobin concentrations and white blood cell counts are available, but not serum electrolyte concentrations nor arterial blood gas contents. Because there were no pathologic nor microbiologic services available, only patients who had typical operative findings of antimesenteric perforation of the distal ileum and a pre-perforation history consistent with typhoid fever were included.

In total, 221 cases were identified. First, 195 cases operated on between January 1, 1978 and December 31, 1989 were reviewed retrospectively. Based on the results of this review, changes in management were instituted. All subsequent patients with typhoid ileal perforation were treated in a prospective fashion with two-layer transverse closure of the perforation and with a course of chloramphenicol, gentamycin, and metronidazole. Chloramphenicol was administered intravenously at 50 mg/kg/

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day up to an adult dose of 2 g daily in divided doses. Gentamycin was administered intravenously at 3 mg/kg/day in divided doses. Metronidazole was administered by rectal suppository at 50 mg/kg/day up to an adult dose of 2 g daily in divided doses. The route of administration of chloramphenicol and metronidazole was changed to oral when the patients began oral intake. Antibiotics were continued for a total 7- to 14-day course.

Using this regimen, an additional 26 patients were treated between January 1, 1990 and May 31, 1991. Statistical analysis of the results was performed by chi square and the Student's t test for unpaired data.

Results

Retrospective Review

Demographic Data. There were 139 (71%) male and 56 (29%) female patients. The mortality rate was higher in females (43% *versus* 27%) (chi square = 4.17, $p < 0.05$). Patients ranged in age from 2 to 72 years, with a mean age of 16.7 ± 13.4 years (standard deviation [SD]). There were 74 patients younger than 10 years, 89 patients between 10 and 29 years of age, and 32 patients older than 30 years of age. The mortality rate was lower in the 10- to 29-year-old age group (21%) when compared with children (36%) and older adults (49%) (chi square = 8.64, *df* = 2, $p < 0.025$).

Presenting Signs and Symptoms. The most common presenting symptoms were fever (78% of patients), abdominal pain (77%), vomiting (38%), diarrhea (25%), and constipation (16%). The mortality rate was higher in patients presenting with constipation (50%) (chi square = 5.24, $p < 0.025$). The most common presenting signs were abdominal tenderness to palpation (84%) and distention (58%). The mortality rate was lower in 34 patients with tenderness localized to the right lower quadrant (18%) than in 15 patients with generalized tenderness (53%) (chi square = 5.40, $p < 0.025$).

Laboratory Investigations. White blood cell counts (WBC) were measured in 92 patients. Mean WBC was 10,870 ± 5510 cells/mm^3 (SD) (range, 3000 to 29,000). Mean WBC was significantly higher in survivors (11,500 ± 5650) when compared with nonsurvivors (8960 ± 4710) (Student's t test, $p < 0.05$).

At least one hemoglobin concentration was obtained on 142 patients. To evaluate the effect of anemia, the lowest hemoglobin value was chosen if more than one was available on a given patient. Mean nadir hemoglobin was 9.1 ± 2.9 g/dL (range, 3.0 to 17.1). There was no difference between the lowest hemoglobin values of survivors (9.3 ± 2.7) and nonsurvivors (8.5 ± 3.4).

There were 26 patients transfused among 46 patients with hemoglobin concentrations less than 8 g/dL. There was no improvement in mortality rate among transfused patients (38%) compared with nontransfused anemic patients (35%).

Radiographs of the abdomen were performed on 109 patients. Eighteen patients had normal radiographs, 34 demonstrated an ileus pattern, and 57 demonstrated free intra-abdominal gas on their radiographs. There was no difference in mortality rate among these groups.

Widal tests (serum agglutinin against the O antigen of *Salmonella typhi*) were performed on eight patients and were positive in all.

Prior Antibiotics. Sixty-six patients (39%) were seen as outpatients before their perforations. Seventeen of these patients received oral chloramphenicol for a presumptive diagnosis of nonperforated typhoid fever. The mortality rate in these patients (29%) was not different from that in those who did not receive such treatment (31%).

One hundred forty patients (72%) received at least one dose of a preoperative antibiotic (131 cloramphenicol, 9 other drugs). Mortality rate remained at 31% whether or not such antibiotics were administered.

Operative Findings. Most patients had only one perforation. Increased number of perforations was associated with worsened mortality rate (chi square = 14.11, *df* = 3, $p < 0.005$) (Table 1).

The perforations all were located on the antimesenteric border of the ileum, ranging from the ileocecal valve to 80 cm proximally, with a mean location of 24 cm proximal to the ileocecal valve.

The degree of fecal contamination was assessed intraoperatively, with 81 patients having minimal contamination (peritoneal exudate limited to one quadrant of the abdomen with no actual fecal spillage) and 114 having gross contamination (peritoneal exudate extending through more than one quadrant or any fecal spillage). The mortality rate was higher in the group with gross contamination (39% *versus* 20%) (chi square = 7.67, $p < 0.01$).

Operative Procedure. Simple plication of the perforation with a one-layer transverse closure was performed in 115 patients, and a two-layer closure was performed in 63 patients. Two patients had such extensive damage to the bowel that a small bowel resection was necessary. Fifteen patients underwent an unspecified type of closure. There was a significant reduction in mortality rate when two-

TABLE 1. *Number of Perforations* Versus *Mortality*

Perforations	Patients	Deaths	Mortality (%)
1	153	42	27
2	26	8	31
3	8	4	50
≥4	8	7	88*

* Chi square = 14.11 (*df* = 3), $p < 0.005$.

layer closure was used (17%) compared with single-layer closure (38%) (chi square = 7.30, $p < 0.01$). There was no difference between the one- and two-layer closure groups in their age or sex distributions, presenting signs or symptoms, presenting WBC, number of perforations, or degree of peritoneal contamination.

The improvement in mortality rate for two-layer closure remained significant when the early deaths (<24 hours after operation) were subtracted. Of 102 single-layer closure patients, 30% died, compared with 12% of 59 two-layer patients (chi square = 6.12, $p < 0.025$).

Postoperative Antibiotics. All patients received chloramphenicol. Forty-four per cent received this antibiotic alone. Thirty-eight per cent also received ampicillin, 31% metronidazole, 10% gentamycin, 8% penicillin, and 4% other antibiotics. All except metronidazole were given intravenously until the patients could resume oral intake, at which time the route of administration was changed to oral. Metronidazole was administered by rectal suppository during the *nulla per os* period. Gentamycin was administered only by the parenteral route.

There was a significant reduction in the mortality rate with broader-spectrum antibiotic coverage in the form of chloramphenicol with gentamycin, metronidazole, or both. The mortality rate was 20% of the 66 patients receiving such a regimen, compared with 36% of the 86 patients receiving chloramphenicol alone (chi square = 4.09, $p < 0.05$). There was no difference between the chloramphenicol group and the chloramphenicol, gentamycin, metronidazole group in their age or sex distribution, presenting signs or symptoms, presenting WBC, number of perforations, or degree of peritoneal contamination. The addition of other antibiotics to the chloramphenicol, gentamycin, metronidazole regimen did not improve prognosis. The addition of antibiotics other than gentamycin or metronidazole to chloramphenicol did not improve prognosis compared with chloramphenicol alone.

The combination of chloramphenicol with metronidazole and gentamycin was used in 15 patients and resulted in the lowest mortality rate (13%). This was not statistically different from the combination of chloramphenicol with either gentamycin or metronidazole alone, however, as used in 51 patients with a mortality rate of 22%.

TABLE 2. *Antibiotics and Degree of Peritoneal Contamination* Versus *Mortality*

Antibiotic	Patients	Deaths	Mortality (%)
Minimal contamination			
Chloramphenicol	40	12	30
CGM	26	1	4*
Gross contamination			
Chloramphenicol	46	19	41
CGM	40	12	30

* Chi square = 5.26, $p < 0.025$.
CGM, chloramphenicol with gentamycin, metronidazole, or both.

TABLE 3. *Antibiotics and Type of Surgical Repair* Versus *Mortality*

Treatment	Patients	Deaths	Mortality
Chloramphenicol, one layer	64	26	40
CGM, one layer	33	9	27
Chloramphenicol, two layers	12	2	17
CGM, two layers	30	4	13*

* Chi square = 8.61 ($df = 3$), $p < 0.05$.
CGM, chloramphenicol with gentamycin, metronidazole, or both.

The protective effect of broader-spectrum antibiotics was most significant in the minimal contamination group (chi square = 5.26, $p < 0.025$) (Table 2). When the type of closure and postoperative antibiotic regimen were considered together (Table 3), there was a progressive improvement in survival with the addition of double-layer closure to broader-spectrum antibiotics (chi square = 8.61, $df = 3$, $p < 0.05$).

Complications. The most frequent complications were wound infection (21% of patients), enterocutaneous fistula (5%), fascial dehiscence (4%), intra-abdominal abscess (3%), and pneumonia (3%). Six patients required a second laparotomy for repeat perforation (4) or bowel obstruction (2). Among these complications, mortality rate was increased only by the development of an enterocutaneous fistula, which had an associated mortality rate of 67% (chi square = 3.91, $p < 0.05$). There was no relationship between the development of complications and the antibiotic regimen or the type of operation.

Mortality Rate. The overall mortality rate in this series was 31%. This was significantly affected by female sex ($p < 0.05$), extremes of age ($p < 0.025$), presence of constipation preoperatively ($p < 0.025$), location of peritoneal signs ($p < 0.025$), preoperative WBC ($p < 0.05$), number of perforations ($p < 0.005$) (Table 1), degree of peritoneal contamination ($p < 0.01$), type of operative repair ($p < 0.01$), postoperative antibiotic regimen ($p < 0.05$) (Tables 2, 3), and the development of enterocutaneous fistula postoperatively ($p < 0.05$). It was not influenced by the hemoglobin concentration, preoperative radiologic findings, nor by the use of outpatient or preoperative antibiotics. Mortality rate was higher in the early postoperative period, with 30% of the deaths occurring within 24 hours of surgery.

Prospective Series

Review of the results of the retrospective series in 1989 demonstrated the advantage of two-layer closure and broader-spectrum antibiotic coverage in the form of chloramphenicol, gentamycin, and metronidazole. Therefore, a prospective series was initiated in which all subsequent patients with typhoid ileal perforation received this treatment. The antibiotic regimen was as outlined in the Methods section.

This prospective series included 26 patients treated from January 1, 1990 to May 31, 1991. This group was not different from the retrospective series in any of the prognostic indices of sex or age distribution, presenting signs or symptoms, presenting WBC, number of perforations, or degree of peritoneal contamination. The mortality rate of 8% in this group was lower than the 40% rate for the patients treated with one-layer closure and chloramphenicol alone in the retrospective series (chi square = 7.88, $p < 0.005$) and lower than the 31% mortality rate in the retrospective series as a whole (chi square = 5.16, $p < 0.025$). The mortality rate was not different from that for patients treated by the same method in the retrospective series. There was no difference in the rate of postoperative complications in the prospective compared with the retrospective series.

Discussion

Typhoid fever has become rare in the United States and the developed world, with an annual incidence of 0.2 cases per 100,000 population. It remains a major public health problem in the developing world as a whole and Africa in particular, however, with annual incidences of 540 and 1020 per 100,000, respectively.[12] Furthermore, the increased incidence of *S. typhi* infections in patients with acquired immune deficiency syndrome (AIDS)[13] raises the possibility of a resurgence of typhoid fever in the developed world.

The most lethal complications of typhoid fever are intestinal bleeding and ileal perforations, both arising from necrosis of Peyer's patches in the terminal ileum. Perforation has been reported to occur in 0.9% to 39% of cases,[1,2,14–20] with wide variation, often dependent on geographic location.[14,15] Butler reviewed 15,980 cases of typhoid in the world's literature and reported an overall 2.8% perforation rate.[15]

The preoperative diagnosis of perforation is based on findings of peritonitis in a patient with a history of a prolonged febrile illness. The intraoperative finding of perforation of the antimesenteric border of the terminal ileum is so characteristic that diagnosis can be based on this alone.[7–9,16,21,22] Although serologic and bacteriologic data may be supportive, these are frequently negative. Blood cultures are positive for *S. typhi* in only 3% to 34% of cases of typhoid perforation,[7,8,10,16] and cultures of the stool and peritoneal fluid are usually negative for this organism.[7,16] The Widal serology test is positive in 20% to 75% of cases of typhoid perforation,[2,3,5–10,14,23] but is frequently negative early in the course of the disease.[2] Typical operative findings were the basis for inclusion in the present study.

The treatment of typhoid ileal perforations remains somewhat controversial.[24] Surgery for the treatment of typhoid perforation began in the late 1800s.[25] After the work of Finney[26] and Cushing,[27] surgery became the standard treatment, with mortality rates ranging from 60% to 80%.[28] The introduction of chloramphenicol greatly improved the outcome of nonperforated typhoid fever. A wave of enthusiasm for the treatment of typhoid perforations with chloramphenicol and supportive care without surgery occurred in the early 1960s.[19,29] Despite initial reports of mortality rates of 20% to 30% with such conservative care, the weight of evidence over the last 25 years has been in favor of surgery supplemented with chloramphenicol.[1–11,14–18,20–23,30–34] Spontaneous sealing of the perforation rarely occurs.[2,3,5,7–11,25,31,33,34] The resulting spillage causes gross fecal contamination in 60% to 90% of cases,[9,11,16,23] with such gross contamination decreasing survival.[7] The inability of chloramphenicol to sterilize the bowel contents, even when given before the onset of perforation,[4,7,10,14,18,25] leads to a continued source of sepsis unless surgical closure of the perforation is undertaken. In a review of 2245 cases of typhoid perforation reported in the world's literature, Butler et al. found the overall mortality rate to be 70% with medical treatment and 26% with surgery.[15]

Mortality rates ranging from 20% to 40% are most commonly reported[1,2,4–7,11,30,31] for typhoid ileal perforations. Rates as low as 3% to 9% have been reported from areas in the developing world with better economic conditions, including Mexico,[32] South Korea,[9,33] South Africa,[16] and Hong Kong.[34] Such mortality rates have been achieved by the addition of close electrolyte and blood gas monitoring, intensive care unit nursing, central venous pressure monitoring, and use of total parenteral nutrition.[9,16,20,24,32] Most of these measures are beyond the reach of the majority of hospitals in the developing world, especially in rural areas. Variables that can be manipulated to improve survival in such locations include more aggressive fluid and electrolyte resuscitation,[1,2,18,35] the type of surgical procedure, and the antibiotic regimen. The current study showed significant reduction in mortality rate with changes in the latter two variables.

A variety of surgical procedures have been recommended for treatment of typhoid perforations. In moribund patients, simple drainage of the peritoneum under local anesthesia may be all that is feasible.[5,9,11,23,25,31] The most common definitive treatment for nonmoribund patients has been debridement and simple transverse closure of the perforation, in either one[4,9,23,31] or two layers.[1,2,8,11,14,16,33,34]

In the current series, the mortality rate was reduced by more than half by the addition of a second suture line to the closure. The improvement remained significant even when early deaths were subtracted, patients whose deaths were possibly not related to the exact operative procedure. This strongly suggests an actual prevention of leaks or repeat perforations by a two-layer closure.

More aggressive treatment in the form of wedge resection[6] or small bowel resection[5,9,22] has been recommended. Most authors recommend resection only for severely damaged bowel,[1,2,4,8,11,14,16,33,34] whereas others use it for multiple perforations,[9,22,31] or even as the preferred treatment for any perforation.[5] The greatly increased mortality rate with multiple perforations in the present series (Table 1) suggests that resection may be better treatment for such patients.

The antibiotic of choice for *S. typhi* infection is chloramphenicol. This drug has great efficacy in nonperforated typhoid fever, may decrease the incidence of perforation, and has generally been the only antibiotic used in cases of perforation. Its spectrum does not fully cover the aerobic gram-negative and the anaerobic bacteria associated with perforation of the distal ileum, however. Although effective *in vitro* against *Bacteroides fragilis,*[36] chloramphenicol has been shown to be ineffective in treatment of infections caused by this organism.[37,38] It is also ineffective against many aerobic gram-negative bacilli *in vivo.*[25,36]

Combination of chloramphenicol with agents more effective against anaerobes (metronidazole or clindamycin) and against aerobic gram-negative bacilli (aminoglycosides) would improve the spectrum of coverage needed by patients with ongoing typhoid fever and fecal peritonitis.[28] Results with the combination of chloramphenicol and parenteral metronidazole have been encouraging.[8,14,22,23] In the current series, for reasons of availability and cost, metronidazole was administered via the rectal route, which results in a 60% to 80% bioavailability.[36] There was a significant improvement in survival when either metronidazole, gentamycin, or both were added to the chloramphenicol (Tables 2 and 3). The addition of both would be logical. There might be a tendency to reserve additional antibiotics for more grossly contaminated cases. Improvement in survival was most marked, however, for minimally contaminated cases (Table 2).

The cost of additional antibiotics is moderate. A day's therapy of intravenous chloramphenicol at 500 mg per dose four times per day costs $2.80 (cost to patient for drug itself in an American hospital). A day's therapy of intravenous gentamycin at 80 mg three times per day costs $1.20. Metronidazole at 500 mg intravenously four times per day costs $6.00 daily. Metronidazole by rectal suppository at the same dosage, however, costs only $0.32 daily.

Conclusion

Typhoid fever is still a major health problem throughout the developing world, and one of its major complication is ileal perforation. The typical mortality rate of 30% associated with perforation is unacceptably high, especially in view of the young age of the patients. We recommend two-layer transverse closure of the perforation and treatment with chloramphenicol, gentamycin, and metronidazole. This treatment regimen resulted in a threefold reduction in mortality rate compared with other regimens. Furthermore, such measures are low cost and widely applicable.

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Acute and Chronic Gastrointestinal Manifestations Associated With *Yersinia enterocolitica* Infection

A Norwegian 10-year Follow-up Study on 458 Hospitalized Patients

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The aim of the present study was to elucidate the gastrointestinal manifestations of yersiniosis. During the period 1974 to 1983, *Yersinia enterocolitica* infection was diagnosed in 458 patients, by isolation from fecal samples or by antibody response. At first admission, 184 patients had abdominal pain; 200, diarrhea; 45, vomiting; and 36, weight loss. Ulcerative colitis was diagnosed in 7 patients, Crohn's disease in 2, and unspecific colitis in 11. Mesenteric lymphadenitis or ileitis were found in 43 of 56 patients at laparotomy. The patients were followed for 4 to 14 years (1987). Thirty-eight patients were readmitted with abdominal pain and 28 with diarrhea; these symptoms were significantly correlated with the corresponding symptoms at first admission. Chronic colitis was diagnosed in 4 patients, chronic weight loss in 12. A follow-up inquiry (380 patients) indicated that patients with right iliac fossa pain during the acute infection less frequently developed chronic abdominal complaints. Gastrointestinal symptoms are common in both the acute and chronic stages of yersiniosis. The correlations between acute and chronic symptoms indicate that yersiniosis is a chronic disease. Immunologically competent individuals may profit by fighting the infection in the right iliac fossa. The relationship between yersiniosis and inflammatory bowel diseases may still not be settled.

YERSINIA ENTEROCOLITICA WAS isolated from a patient with acute terminal ileitis in 1964,[1] and its associations with this condition and with mesenteric lymphadenitis were recognized during the next few years.[2,3]

The most common abdominal manifestation of the acute *Y. enterocolitica* infection apparently is a self-limiting gastroenteritis. Emergency intestinal resections have been performed in some patients, however, and some have died of fulminant disease.[4,5] Other patients have developed chronic intestinal disease.[6]

The aim of the present study was to perform a survey of acute and chronic gastrointestinal manifestations associated with *Y. enterocolitica* infection.

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Materials and Methods

The determination of antibodies to *Y. enterocolitica* was introduced in Norway by the National Institute of Public Health in 1972.

During the 10-year period 1974 to 1983, the institute's laboratory diagnosed *Y. enterocolitica* infection in 553 hospitalized patients. Excluded were 95 patients with insufficient or missing hospital files. Adequate clinical information was obtained on 458 patients (202 men and boys, mean age 33.4 years; and 256 women and girls, mean age 39.6 years) admitted to 52 different hospitals, and these patients constitute the material of the present study.

Clinical Data

Clinical data were obtained from the various clinical departments on the first admission, and from all subsequent admissions. Valuable information was obtained also through general practitioners. The study was terminated June 30, 1987, with observation times of 4 to 14 years. At this time, 46 patients were dead and two could not be located.

Three hundred eighty of the 410 remaining patients replied to a clinical questionnaire on persistence or development of particular abdominal complaints *after* the infection, by checking as appropriate the alternatives "Yes," "No," or "Uncertain." The patients admitted to Bergen University Hospital all underwent a thorough clinical follow-up examination, including endoscopic examinations in patients with severe chronic diarrhea.

Diagnosis of *Y. enterocolitica* infection was based on one or both of the following methods:

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A. Isolation of Y. enterocolitica from fecal samples (serotype 0:3, 56 patients; serotype 0:9, 1 patient).

B. Antibody response to *Y. enterocolitica* as evaluated by one of the following methods:

(i) During the period 1974 through August 1982: bacterial whole cell agglutination using alcohol-treated bacterial cells as antigen. An agglutination titer of at least 640, or a fourfold or greater increase of the titer in two consecutive samples, was recognized as indicative of an actual or recent infection (serotype 0:3, 395 patients; serotype O:9, 2 patients).

(ii) During the period September 1982 through 1983: enzyme-linked immunosorbent assay (ELISA) using lipopolysaccharide extracted with hot phenol water as antigen.[7] Serum samples were examined for both specific IgG and IgM activity (at follow-up also IgA activity). Net absorbance values (absorbance in the sample minus the absorbance in the negative control) of 0.1 or greater were regarded as significant. A net absorbance of 0.5 or greater, or an increase in the activity of at least 30% in two consecutive serum samples, were considered indicative of an actual or recent infection (serotype 0:3, 33 patients).

Laboratory and Clinical Examinations. Laboratory and clinical examinations were performed according to standard procedures. Their extent varied between hospitals and departments and with seriousness of disease. The reported observations represent minimum numbers.

Statistics

The two-sample Student's t test, the standard error of difference between two proportions, the chi square test with Yates' correction, and Fisher's exact test for 2 × 2 contingency tables (all two-sided) were used for comparison between subgroups of the material.

Results

First Admission

Acute Abdominal Symptoms. Age and sex distribution of patients with acute abdominal symptoms are displayed in Table 1. Patients with particular pain localizations showed significantly different age distributions. The majority of patients with *vomiting,* and every second patient with *diarrhea,* concomitantly had abdominal pain.

Children less than 10 years of age had a significantly higher total frequency of diarrhea than did older patients (17/24 > 183/424; p = 0.015); and a higher relative frequency of macroscopically bloody diarrhea (5/17 > 14/183; p = 0.03). Most children with bloody diarrhea were infants. Children younger than 10 years of age had a significantly higher frequency of vomiting than did older patients (6/24 > 39/424; p = 0.04); all children with vomiting were in fact younger than 5 years of age.

Weight Loss. Weight loss (mean, 7.4 kg) in 36 patients usually took place over a few weeks or months in association with the acute infection. Twenty-four patients concomitantly had diarrhea; 19, acute polyarthritis; 4, liver involvement; 2, acute nephritis; and 1, pulmonary involvement. Four female and 2 male patients lost more than 10 kg of weight. A 26-year-old woman who lost 20 kg over 1 year developed chronic pancreatic insufficiency.

Emergency Operations. Thirty males (14.9%) and 26 females (10.2%) underwent emergency abdominal operations. Perioperative findings and age distribution of patients are displayed in Table 2.

TABLE 1. *Acute Abdominal Symptoms Observed Among 448 Patients Admitted With* Y. enterocolitica *Infection**

	M				F			
		Age (yr)				Age (yr)		
	No.	Range	Mean	SD	No.	Range	Mean	SD
Abdominal pain								
Diffuse	40	2–66	32.6*	17.2	52	3–81	39.1‡	18.5
Low right	36	6–88	27.1†	17.9	38	7–68	30.9‡	16.8
Subcostal right	7	35–60	46.1*†	9.2	8	19–94	41.6	24.2
Left side	2	33–36			1	47		
Total	85				99			
Diarrhea								
Without bleeding	80	1–88	34.0	18.9	101	0–81	41.3	18.3
Bloody	9	0–65	30.7	21.2	10	0–55	23.8	18.0
Total	89				111			
Vomiting	21	2–77	25.4	18.2	24	0–94	40.5	22.9
Weight loss	14	15–68	33.4	14.6	22	6–75	50.9	17.2

Ten patients with previous ulcerative colitis, Crohn's disease, or chronic colitis not included.

* p = 0.05.

† p < 0.01.

‡ p < 0.04.

TABLE 2. *Intra-abdominal Conditions Observed in 56 Patients who Underwent Emergency Laparotomy*

	M				F			
		Age (yr)				Age (yr)		
	No.	Range	Mean	SD	No.	Range	Mean	SD
Mesenteric lymphadenitis	10	6–23	14.6*†	5.0	13	7–47	23.2*‡	11.5
Terminal ileitis/ileitis	14	17–66	31.5†	12.4	6	16–66	38.2‡	21.3
Other conditions (see text)	6				7			

Sex and age distribution, significance of observed mean age differences.
* p = 0.04.
† p = 0.0006.
‡ p = 0.06 (NS).

Mesenteric lymphadenitis was the only finding in 10 male and 13 female patients. Among 13 male patients with acute terminal ileitis, eight also had mesenteric lymphadenitis. One male patient had regional ileitis. Among six female patients with ileal affection, three had terminal ileitis and three had diffuse ileitis. The youngest two (16 and 18 years of age) additionally had mesenteric lymphadenitis. One woman with diffuse ileitis shortly afterward developed acute pancreatitis. The sex differences in frequency of ileitis, and in lymphadenitis/ileitis ratio, were statistically not significant.

In two men (18 and 40 years of age) and one woman (23 years of age), surgery disclosed acute appendicitis, an 88-year-old man suffered from acute cholecystitis, two women (17 and 75 years of age) had acute hepatitis, and a 35-year-old woman had acute colitis. In a 21-year-old man, mesenteric lymphadenitis was associated with a perforated duodenal ulcer. A 41-year-old man presented with monstrous mesenteric lymphadenitis, splenomegaly, and slight liver affection[8]; in another (57 years of age), mesenteric lymphadenitis caused ileocolic intussusception.[9] An ileopsoas muscle hematoma was found in a 22-year-old woman; in another (20 years of age), ample intraperitoneal fluid only was found.

Examinations and Findings in Patients Not Operated On. Thirty-two patients underwent endoscopy, and 137 were radiologically examined. Acute gastroduodenitis was diagnosed in one patient, terminal ileitis in one, acute colitis in seven, acute proctitis in two, and chronic unspecific colitis in two patients.

Abdominal Masses. A boy and a man (14 and 26 years of age) and three women (19, 42, and 80 years of age) were admitted with right iliac fossa inflammatory masses, and a 66-year-old man was admitted with a rectovesical fossa abscess.

Association With Chronic Inflammatory Bowel Disease. A 30-year-old woman was admitted 1 month after the acute onset of severe diarrhea; a 32-year-old man was admitted after 7 months. Both patients later underwent bowel resection. Microscopy of specimens showed changes consistent with ulcerative colitis (UC) in the woman, and Crohn's disease (CD) in the man.

Another four men (19 to 74 years of age) and three women (41 to 62 years of age) had suffered from chronic inflammatory bowel disease for 2 to 20 years. Ulcerative colitis was diagnosed in six; CD, in 1. Some of them had experienced extraintestinal manifestations like eosinophilic pulmonary infiltrate, hepatitis, chronic cholecystitis, rectovaginal or perianal fistulas, arthritis, eye inflammation, or generalized urticaria; one had positive tests for rheumatoid factor. One patient died in hospital, three underwent intestinal resections, and three were still on medical treatment at follow-up. Chronic nonspecific colitis was diagnosed in a 48-year-old woman with chronic diarrhea.

Follow-up

Readmissions. One hundred sixty patients (73 males, 36.1%; and 87 females, 34.0%) were readmitted during the follow-up period; 47 male and 55 female patients were readmitted three or more times. One male and 1 female patient were admitted about 40 times each because of chronic disease affecting several organ systems.

Abdominal symptoms. Among the 160 readmitted patients, 38 suffered from chronic abdominal pain, and 28 from chronic diarrhea. Nine patients suffered from both abdominal pain and diarrhea. Symptoms at readmission were significantly correlated with symptoms at first admission (Table 3).

Weight loss (mean, 9.4 kg) was observed in 12 patients (5 males and 7 females); it was associated in all with some chronic manifestation such as diarrhea, nephritis, hepatitis, or arthritis. Three of these patients had also experienced weight loss in association with the acute infection. A woman who lost 24 kg needed intravenous alimentation.

Examinations and findings. Thirty-three patients underwent endoscopy, and 53 were radiologically examined. Chronic colitis was diagnosed in another four male patients (mean age, 30 years). A 36-year-old man with diffuse abdominal complaints and abnormal stools had low serum levels of iron, cholesterol, and cobalamin. His duodenal biopsies showed low and partly coalesced villi, sug-

TABLE 3. *Patients With and Without Acute Abdominal Pain or Diarrhea at First Admission who Were Readmitted With Chronic Abdominal Pain or Diarrhea*

First admission		Readmission symptoms			
		Abdominal pain		Diarrhea	
Symptom	No.	No.	(%)	No.	(%)
Abdominal pain					
With	184	23	(12.5)*	15	(8.2)
Without	264	15	(5.7)*	13	(4.9)
Diarrhea					
With	200	22	(11.0)	18	(9.0)†
Without	248	16	(6.5)	10	(4.0)†
Total	448	38	(8.5)	28	(6.3)

Ten patients with previous ulcerative colitis, Crohn's disease, or chronic colitis not included.

* $p < 0.015$.

† $p = 0.03$.

gesting celiac disease; gastric biopsies showed chronic inflammation and intestinal metaplasia, and colonic biopsies showed slight chronic inflammation. Two patients had pathologic Schilling's tests, indicating ileal affection.

Reexamination at the Bergen University Hospital. Among 24 reexamined patients, nine complained of diarrhea; they all related the start of their complaints to the *Y. enterocolitica* infection.

Five with severe chronic diarrhea (5 to 15 stools a day) underwent duodenoscopy and colonoscopy; in four of them duodenal biopsies were abnormal with slight edema, moderate inflammation, and some flattened villi. One patient microscopically had minor changes in distal colon. Small bowel series disclosed no abnormality; serum levels of folic acid, cobalamin, calcium, and total protein were normal in all. *Y. enterocolitica* or other pathogenic bacteria were not isolated from their stools. All still had significant specific activity of IgG (net absorbance values: 0.25 to 0.57), three had low but significant IgM activity, and three had IgA activity. One patient had an IgA net absorbance value of 0.25 after 12 years; another, 0.61 after 9 years (ELISA).

Questionnaire. Chronic complaints inquired about were abdominal pain, diarrhea, mucous or bloody diarrhea, voluminous stools floating on water, and weight loss.

The frequencies of "Yes" answers among 371 patients without inflammatory bowel disease (IBD) (see above) are displayed in Table 4. The complaints usually were tolerable and experienced periodically, but several patients (among them 11 with weight loss) had needed hospital admission, and some were socially disabled.

Sex and age. Male and female patients reported comparable frequencies of the particular complaints; the age distributions mirrored the sexes' whole material age distributions. No correlation was found between age at first admission and frequencies of later complaints.

Time of observation. Patients who had been followed for 10 years or more reported higher frequencies of mucous or bloody stools, and of weight loss, than patients admitted later ($38/213 > 17/158$, $p < 0.06$; *viz.* $28/213 > 11/158$, $p < 0.06$).

Relation to first admission symptoms. More patients complained of diarrhea who had been admitted with abdominal pain, than did patients admitted without abdominal pain ($69/158 > 70/213$; $p < 0.035$).

Patients admitted with diffusely located abdominal pain reported higher frequencies of mucous or bloody diarrhea, voluminous stools floating on water, and of unintentional weight loss than did patients with right iliac fossa pain. A high frequency of voluminous stools was reported by pa-

TABLE 4. *Follow-up Results: Chronic Abdominal Symptoms Among 371 Patients Without Previous Inflammatory Bowel Disease*

First admission		Chronic complaints							
		Diarrhea without bleeding		Mucous or bloody diarrhea		Voluminous floating stools		Weight loss	
Symptom	No.	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Abdominal pain									
Without pain	213	42	(19.7)	28	(13.1)	30	(14.1)	18	(8.5)
Diffuse	81	18	(22.2)	19	(23.5)*	16	(19.8)†	15	(18.5)‡
Right iliac fossa	62	17	(27.4)	6	(9.7)*	5	(8.1)†§	4	(6.5)‡
Right subcostal	12	5	(41.7)	1	(8.3)	6	(50.0)§	2	(16.7)
Left side	3	2		1		2		0	
Diarrhea									
None	201	35	(17.4)	26	(12.9)	31	(15.4)	20	(10.0)
Without bleeding	154	48	(31.2)	24	(15.6)	26	(16.9)	18	(11.7)
Bloody	16	1	(6.3)	5	(31.3)	2	(12.5)	1	(6.3)
Total	371	84	(22.6)	55	(14.8)	59	(15.9)	39	(10.5)

* $p < 0.035$

† $p = 0.05$

‡ $p = 0.035$

§ $p = 0.003$

tients with right-sided subcostal pain. More patients complained of diarrhea who had been admitted with diarrhea, than did patients admitted without diarrhea (78/170 > 61/201; $p < 0.0025$).

Clinical Course of Patients With Ileal Affections. The 21 patients with verified terminal or regional ileitis all replied to our questionnaire. None had developed CD; neither had this group experienced more abdominal complaints than other patients. Three male patients were examined by small bowel series after 5 years, with normal findings. *Y. enterocolitica* had been isolated from stools in two patients during the acute infection, and antibody titers of 5000 had been recorded in two.

Discussion

Acute Abdominal Manifestations

Previous reports state that abdominal pain is common during acute *Y. enterocolitica* infection. Attention has been paid to "the right iliac fossa syndrome"[2–4,10,11]; and one of us has described "the right subcostal syndrome" mimicking cholecystitis.[12] The present study supports these observations, regarding both frequency and localization of abdominal pain. Diarrhea is a common acute manifestation at all ages,[4,10,11] but macroscopically bloody diarrhea is especially seen in infancy and childhood.[13–15] The present study concurs with the previous ones; and we have been able to show the statistical significance of the age distribution. In accordance with previous reports, "the right iliac fossa syndrome" was the most common indication for emergency surgery, which regularly disclosed mesenteric lymphadenitis or ileal affection.[1–3,10,11] The significant difference between age distributions of male and female patients with mesenteric lymphadenitis has no counterpart in previous reports. Clinical studies indicate that the *Y. enterocolitica* infection may cause acute appendicitis; but it is responsible in only a minor fraction of the total number.[2,16,17] The appendicular inflammation is generally slight.[1,16] We abstain from causative conclusions in our three cases, because isolation of *Y. enterocolitica* was not attempted. Findings of perforated duodenal ulcer and acute cholecystitis possibly may represent coincidences; abdominal masses in unoperated patients may represent conditions like those found in patients who underwent surgery.

Chronic Abdominal Manifestations

At readmission, every third patient complained of abdominal pain or diarrhea; these symptoms were significantly correlated with the corresponding symptoms at first admission. Twelve patients suffered from chronic weight loss. In a few patients, the substrates of these complaints might have been traced by the demonstration of chronic colitis, duodenal microscopic changes, or abnormal Schilling tests.

At follow-up, chronic abdominal complaints were common even among patients who had not consulted a doctor, and significant correlations were demonstrated between pain localization at first admission and frequencies of particular complaints. The higher frequencies among patients with long-time observation might indicate development over several years.

Reexamination of the Bergen University Hospital patients confirmed the frequencies of abdominal complaints claimed by questionnaire responders. Duodenal microscopic changes in four of five patients with severe diarrhea are in accord with findings in one of the readmitted patients (see above), and with a previous report on duodenal affection associated with weight loss and arthritis.[18]

In keeping with our observations are several previous reports of sustained or recurrent diarrhea, or abdominal pain, after *Y. enterocolitica* infection.[4,11,12,18] An association between the *Y. enterocolitica* infection and chronic colitis or UC was suggested from clinical observations 15 years ago[19,20]; later, high frequencies of specific antibodies were observed among patients with UC[21] and CD,[22] and recently persistence of virulent *Y. enterocolitica* has been demonstrated in patients with chronic intestinal inflammations.[23]

Ulcerative colitis had been diagnosed in six of our patients several years before the diagnosis of *Y. enterocolitica* infection. This prevalence of UC significantly exceeds the highest prevalence previously estimated in the Scandinavian countries (6/458 > 741/807.000; $p < 0.000001$).[24] Some of our patients with IBD may have acquired *Y. enterocolitica* infection in an already diseased state. Two patients, however, were admitted shortly after the acute onset of diarrhea; they both underwent bowel resection. These observations may support the concept of a connection between the *Y. enterocolitica* infection and IBD.

Patients admitted with right iliac fossa pain had the better prognosis regarding future mucous or bloody stools, voluminous stools floating on water, and unintentional weight loss. It may be supposed that different pain localizations represent involvement of different organs. Given that right iliac fossa pain represents mesenteric lymphadenitis or terminal ileitis, the patients who are immunologically capable of fighting the microorganism at this early line of defense will profit. If a connection between *Y. enterocolitica* infection and IBD exists, the hypothesis also may explain why patients with *Y. enterocolitica* infection and verified acute terminal ileitis infrequently develop CD at a later time[25,26]; and it might be in accordance with the hypothesis that development of IBD involves an interaction between external agents, immunologic genetic influences, and host response.[27] Ulcerative colitis and

Crohn's disease may be prototypes, or polar extremes, of a single disease also comprising indeterminate colitis.[27,28]

Weight loss was experienced by 73 patients, (27 males, 46 females; 16.3%). Forty-five were admitted to hospital; another 28 reported this complaint at follow-up. Correspondingly, a previous report states that 6 of 37 patients (16%) in a gastroenterologic unit lost weight[4]; the symptom also has been noticed by others.[18,29] Weight loss may be associated with bowel affection and diarrhea, but also with extraintestinal or systemic disease without diarrhea.

Conclusion

The present study supports previous observation on gastrointestinal affection during acute *Y. enterocolitica* infection, and indicates that the infection may launch chronic abdominal complaints. The relationship between the *Y. enterocolitica* infection and indeterminate colitis, UC, and CD still may not be definitively settled. Further prospective studies are required to elucidate the role of *Y. enterocolitica* in chronic gastrointestinal disease.

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Splenic Autotransplantation and the Immune System

Adequate Testing Required for Evaluation of Effect

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The risk of severe infections after splenectomy, even after many years, is now well established. In attempts to prevent these infections, spleen-saving techniques, including autotransplantation of spleen fragments, have been performed, when possible in combination with vaccination. The problem in autotransplantation is the evaluation of functional activity. The results of the tests used until now often do not seem to correlate very well with the risk of developing an overwhelming postsplenectomy infection (OPSI). This may be related to the fact that the tests used evaluate general functions, and not specific spleen-related functions, such as the capacity to mount a primary response to certain polysaccharide antigens present in the capsule of bacteria known to cause OPSI. In this review, the significance of the spleen in the human immune system is discussed and the effects of splenectomy are described, including the precautions that can be taken to diminish the risk of postsplenectomy infections and sepsis. It appears that postsplenectomy vaccination is more successful when recently developed protein-conjugated polysaccharide vaccines are used. Because the present testing of the function of spleen autotransplants is not adequate, we suggest that new tests should be developed, employing appropriate polysaccharide antigens.

FOR MANY YEARS, the spleen has been considered a mysterious and rather useless organ. Consequently, surgical removal of the spleen because of trauma or disease was thought to have negligible consequences for the health of the patient (for a historical review, see ref. 1). Although incidental reports mentioned a relationship between splenectomy and infection, it was not until 1952 that a causative association was reported between splenectomy (for congenital hemolytic anemia) and the occurrence of meningitis with sepsis.[2] Since then, the increased risk of infection and septicemia directly related to splenectomy has been well defined in the literature. Such infections are now generally termed overwhelming postsplenectomy infections (OPSI). Although most infections occur within the first few years after splenectomy, the risk of OPSI is lifelong.[3] The highest incidence of OPSI is found in infancy and childhood. Patients who have undergone splenectomy for hematologic diseases, reticuloendothelial diseases, or portal hypertension have a higher incidence of OPSI than those undergoing splenectomy for trauma.[4–7]

Because the spleen is an important organ of the immune system, splenectomy has several effects on human immune functions. One of the surgical techniques employed to overcome these effects is the autotransplantation of splenic fragments. A crucial point in evaluating the effect of splenic autotransplantation is the use and development of adequate tests for those functional activities that cannot be taken over by other tissues of the lymphoid system.

In this report, we will review the role of the human spleen in the immune system, as well as the effects of splenectomy, and techniques to prevent postsplenectomy problems. This is followed by a perspective view on functional testing of spleen autotransplantation now and in the future.

The Spleen as a Part of the Immune System

Because of the central position in the bloodstream and the large blood supply of about 5% of the blood volume per minute, the spleen represents an important meeting point between antigenic information transported by the blood and the immune system. It possesses a wide range of the immune cell repertoire, and its specific architecture allows unique functions. Two major critical functions of the spleen can be recognized: it serves as a large phagocytic filter and it is a major antibody-producing organ.

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Phagocytosis of foreign particles can be promoted by interaction with opsonins, serum factors that enhance their uptake by specific phagocytosing cells. The spleen has a prominent role in the generation of opsonins.[8,9] Splenic phagocytes, together with macrophages in the liver, synthesize the majority of components of the classical pathway of complement.[9] Generation of specific antibody is primarily dependent on the spleen. The role of the spleen in phagocytosis of foreign particles is particularly important for nonopsonized or badly opsonized particles. Whereas the mononuclear phagocyte system (MPS) in the liver is the main site of phagocytosis of opsonized particles, the spleen is the major organ for the phagocytosis of nonopsonized particles. In experiments in rabbits, the phagocytosing capacity for nonopsonized particles appeared 60 times as effective in spleen as in liver when corrected for weight.[9] The unique microvasculature of the spleen supposedly contributes to the specialized function of the spleen in the phagocytosis of insufficient opsonized particles.[10,11] The greatly retarded blood flow in the red pulp cords allows a very intimate and prolonged contact between antigens and phagocytes. Thus, particles can be ingested without specific ligand–receptor interactions. An important practical implication of this specialized phagocytosing capacity is that the spleen is the most important site of clearance in the early phase of bacterial invasion, before sufficient amounts of specific antibody have been produced.

Another special feature of the spleen is the generation of tuftsin, a tetrapeptide reported to exert stimulatory effects on activity and migration responses of phagocytic cells.[4,12]

The spleen is the site of M immunoglobulin (IgM)-specific antibody generation very early after exposure to blood-borne antigen. The first contact of antigens entering the spleen through the blood and immunocompetent cells occurs in the marginal zone,[13] a structure exclusively present in the spleen.[14-16] This marginal zone is unique in its microvasculature, enabling a very low blood flow, and in the presence of specialized macrophages/antigen-presenting cells and a subset of intermediate-sized B cells with a specific phenotype: IgM+, IgD+, and strongly CD21+.[14-16] Although in other lymphoid tissues B cells with this phenotype can be found, the splenic marginal zone contains the largest accumulation of this type of B cells in the body. When the blood enters the marginal zone sinusoids, there is a considerable increase in diameter, with a subsequent decrease in blood flow. Similarly as in the red pulp, a sluggish flow results; this enables a close contact between antigens and phagocytes or lymphoid cells, and between different cell subtypes involved in the immune response.[10,11]

Because the spleen is a major lymphoid organ, it also plays an important role in the primary and secondary immune response. The spleen is specifically involved in the immune response to thymus-independent antigens type 2 (TI-2 antigens). These antigens, generally polysaccharides, are the antigenic component of the capsule of encapsulated bacteria as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitides.* The immune response to TI-2 antigens is characterized by the need of T-cell–produced factors, although it is independent of the actual presence of T cells.[17] After splenectomy, this response is significantly decreased or even absent. The initiation of the response to polysaccharide antigens (TI-2 antigens) takes place in the splenic marginal zone. In rodents, TI-2 antigens were found to localize specifically on antigen-presenting cells in the marginal zone (MZ),[18] and the elimination of MZ cells abrogated the immune response to such antigens.[19] As described above, marginal zone B cells have a distinct immunophenotype. Whether MZ B cells play a special role in the immune response to TI-2 antigens, over and above the general role of B cells in the humoral immune response, is yet unclear.

Effects of Splenectomy

Once the role of the spleen in host defense had been recognized, the immunologic consequences of splenectomy were given more attention. Postsplenectomy infections are nearly always caused by encapsulated bacteria, such as *S. pneumoniae, H. influenzae,* and *N. meningitides.* It appeared that, after splenectomy, there is a significant decrease in the primary immune response to bacterial capsular polysaccharide antigens.[4,6,20,21] These antigens belong to the group of TI-2 antigens, and other antigens of this type also give a similar decreased immune response after splenectomy.[22-25] Besides the impaired response to TI-2 antigens, a variety of other effects of splenectomy on the human and animal immune system has been described,[4,6-10,26,27] summarized in Table 1.

Precautions in Relation to Overwhelming Postsplenectomy Infections

From the time the OPSIs were recognized to be related to splenectomy, it still took several years before attempts were made to diminish this risk of infection. One approach has been the introduction of spleen-saving techniques,

TABLE 1. *Effects of Splenectomy on the Immune System*

Reduced phagocytic activity, in particular with respect to nonopsonized particles
Prolonged residence time of lymphocytes in the blood
Decreased serum IgM
Reduced alternative complement pathway activity
Decreased tuftsin formation
Increased autoantibody activity
Diminished numbers of suppressor T cells

such as partial splenectomy, splenorrhaphy or autotransplantation of spleen tissue fragments in the abdomen.[28–30] The latter technique was introduced based on the observation of splenosis: the persisting presence of small parts of viable spleen tissue in the abdomen after splenectomy for trauma. As a consequence of this observation, experiments have been performed leaving spleen tissue deliberately in the abdomen after splenectomy, mostly in an omentum pouch.

The effects of partial splenectomy and splenorrhaphy have been demonstrated to be beneficial. Compared with nonsplenectomized controls, there was no decrease in immunologic functions. Also, in long-term follow-up studies, no differences were found in incidence of infections.[1,26,28,31]

In contrast, reports on the effects of autotransplantation of spleen fragments are controversial.[7,26] Although beneficial effects have been reported,[28,32,33] several other studies observed no significant differences compared with splenectomized patients without splenic regrowth.[34–37] Several factors may account for this. First, the total amount of blood that is filtered is low, despite an acceptable vascularization. Second, the microanatomy of the splenic fragments is probably not suited for the specific local low flow that is characteristic for the normal spleen and is essential for the close contact between antigen and phagocytes and immunoresponsive cells. Third, for testing of the immune function of the autotransplanted spleen fragments, two items have to be evaluated: phagocytosing capacity, with special attention to nonopsonizing or badly opsonizing antigens, and (humoral) immune response capability, with particular attention to TI-2 polysaccharide antigens. With respect to these items, the presently used tests of the function of the autotransplanted spleen fragments may not be adequate for evaluation of the ability of the fragments to perform real "splenic" immune functions, as will be discussed later.

Because *Streptococcus pneumoniae* is the most frequent cause of OPSI, vaccination with pneumococcal polysaccharide vaccine (Pneumovax; Merck Sharp & Dohme, West Point, PA) has been used, in combination with spleen-saving techniques. Pneumococcal polysaccharide (PPS) vaccine (Pneumovax) contains polysaccharide antigens of several (presently 23) strains of pneumococci. The reported results of this vaccination are variable.[5,20,38–41] When it is possible to vaccinate before splenectomy (in case of elective splenectomy), an adequate antibody response is obtained. In case of vaccination after splenectomy (*i.e.*, in most cases), good antibody responses have been reported. Despite this, several postvaccination cases of OPSI have been observed.[3,42,43] This can be explained by the fact that generally only total antibody response to all pneumococcal subtypes is taken into account. In studies reporting the response to different subtypes separately, some of these subtype PPS appear to be particularly nonimmunogenic after splenectomy or in early infancy and do not provoke an adequate antibody response.[3,5,20,21,38–40,42–44] A possibility is also that the antibodies to PPS that are present are not capable of good opsonization (lack of certain factors, *e.g.*, tuftsin). As the spleen is also the site for phagocytosis of poorly opsonized antigens, the absence of this organ may subsequently cause an increased risk of OPSI.

How can the difference in postsplenectomy immune response to PPS subtypes be explained? The specific relationship between the immune response to TI-2 antigens and the presence of an intact spleen holds true for neutral, but not for charged, polysaccharides, as in particular neutral polysaccharides localize on MZ antigen-presenting cells and elicit an almost exclusively spleen-related immune response.[18,22–24,45–47] For certain subtypes of PPS antigens, this relationship also has been demonstrated.[21] It can be concluded that only a subset of (neutral) polysaccharide antigens are in fact true TI-2 antigens. In future studies, it should be evaluated whether the poorly responding vaccine subtypes consist of neutral polysaccharides, and the well-responding subtypes consist of "nonneutral" polysaccharides. The mechanism that results in the fact that neutral polysaccharides are presented by MZ antigen-presenting cells only, is presently unknown. Humphrey[24,45] suggested that absence of charge together with inability to activate C3 spontaneously may be an essential property.

Recently, vaccines have been developed of bacterial polysaccharide (*Haemophilus influenzae*) conjugated to protein vaccines as tetanus toxoid.[48–52] The response to these vaccines and the long-term effect in infancy is far better than that to polysaccharide vaccine alone. The findings suggest that when presplenectomy vaccination is not possible, unconjugated bacterial polysaccharide vaccine is inadequate[24] and should be replaced by a protein-conjugated vaccine. Similarly, vaccination of infants younger than 2 years is probably only useful when a protein–polysaccharide conjugate vaccine is used.

Functional Testing of Spleen Transplants

In testing of the immune function of the splenic fragments, most attention is given to phagocytic cells. Testing is mostly performed using irradiated erythroid cells, which are generally well opsonized. This is not an adequate test for the presence and function of splenic phagocytes, which, in their microenvironment, are specifically characterized by their ability to phagocytose poorly opsonized antigens. Moreover, there is not really a need for well-opsonized antigen-phagocytosing cells, because the mononuclear phagocyte system of the liver has by far enough capacity to take care of that function. A possibility to overcome the problem of using well-opsonized particles is to use methods in which damaged erythroid cells are selectively coated with a very low concentration of immunoglobulin, causing "a low grade of opsonization," which is too low for adequate phagocytosis by nonsplenic parts of the mononuclear phagocyte system.[53]

Further, and probably more relevant, little attention is given to the immune response capabilities. Most problems after splenectomy are caused by encapsulated bacteria, which in healthy individuals elicit a response directed to capsular polysaccharide (TI-2) antigens. Tests of the immune response capacity employing T-cell–dependent (TD) antigens (as irradiated red cells) seem therefore less useful. The decrease in immune response in splenectomized patients with or without autotransplantation when using TD antigens is fully and simply explained by the decrease in volume and the lack of rapid vascular access of lymphoid tissue after splenectomy. Consequently, a difference between patients with and without autotransplantation cannot be expected when using such antigens.

It should be realized that in case of TI-2 polysaccharide antigens, only the primary response is dependent on the spleen. Therefore, even when small amounts of autotransplanted spleen tissue are present (which often is the case), with adequate response capacities to TI-2 antigens, specific antibodies will be formed. Because these will cause opsonization of the antigen (encapsulated bacteria), phagocytosing capacity of the splenic fragments will not play an important role, because the cells of the mononuclear phagocytosing system in the liver are perfectly capable of removing opsonized particles. In addition, because the secondary response can be taken care of by other lymphoid organs, it should be possible to obtain normal levels of produced antibodies in case of rechallenge. This is of particular importance with respect to vaccination, which in such cases can be expected to be more successful.

In conclusion, it is indicated to devise functional tests of autotransplanted spleen tissue, which include the use of not previously encountered, nonharmful TI-2 polysaccharide antigens, because the inability to mount a response against such antigens most probably is the crucial deficient function in postsplenectomy patients.

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Updating the Management of Salvageable Splenic Injury

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Because of the ready availability of autotransfusers and risk of transfusion-transmitted disease, the authors reexamined the management of splenic trauma. During the past 6 months, 20 adult and pediatric patients were treated for blunt splenic trauma. Nine had "minor" lacerations and were successfully managed nonoperatively. Eleven had ongoing hemorrhage or associated visceral injury necessitating laparotomy. In two, coexistent injuries were life threatening and total splenectomy was performed. The other nine had major splenic trauma that was either an isolated phenomenon or was associated with an injury not jeopardizing survival; eight spleens were salvaged. Mean intra-abdominal blood loss was ~1250 mL and, using a "cell saver," an average of ~790 mL was reinfused. Six received no other blood transfusion whereas three received 2250 mL homologous blood in addition to 4250 mL via the "cell-saver." With hilar laceration, repair was facilitated by temporarily occluding the splenic pedicle atraumatically, and suturing torn polar branches via the laceration site. In both children and adults with major splenic injury, the authors now recommend early laparotomy with reinfusion of autologous blood. The spleen or a large remnant can usually be salvaged, and homologous blood transfusion with its attendant complication can often be obviated altogether.

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OVER THE PAST two decades, major shifts have taken place in the management of splenic trauma. Most children, for example, are now safely treated nonoperatively with the high expectation that intra-abdominal bleeding will abate spontaneously.[1] In both adults and children, in situations where laparotomy has proved necessary either because of ongoing hemorrhage or risk of associated visceral injury, at least 50% of traumatized spleens can be salvaged by repair or partial splenectomy.[2,3] Spleen-sparing either through careful observation or operative repair avoids the small risk of subsequent overwhelming sepsis[4] and other sequelae, both known and unknown, of removal of the spleen.[5,6] Conversely, when the spleen is avulsed or shattered or other life-threatening injuries jeopardize survival, total splenectomy is still appropriate.[2,3,7]

Whereas this balanced approach has become well standardized, there are two recent developments that prompt re-evaluation. First is the rising concern of transmitting viral hepatitis and human immunodeficiency virus infection through blood transfusion. Second is the ready availability of automated "cell savers" that have greatly simplified reinfusion of shed intra-abdominal blood at the time of laparotomy. These two developments, in addition to other technical refinements that increase the likelihood of operative preservation, have stimulated us to report our most recent experience with blunt splenic trauma.

Clinical Studies

From August 1, 1990 to January 31, 1991, 20 patients (10 male; 10 female) with blunt trauma and spleen injury were treated at the Level I Trauma Center at University Medical Center in Tucson, Arizona. Of these, four had "minor" isolated splenic lacerations based on benign clinical findings and abdominal computed tomographic images. These four patients were managed without operation or blood transfusion. Five patients had multiple other serious injuries (*e.g.,* head trauma, fractured pelvis, ribs, extremities) necessitating packed red blood cell transfusions (average, 500 mL), but the spleen injury itself was also treated nonoperatively. Two patients had coexistent life-threatening intra-abdominal injuries necessitating laparotomy, and total splenectomy was considered the safest course of action. The final nine patients (5 male; 4 female) had "potentially salvageable splenic trauma requiring laparotomy," that is, individuals with physical or

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laboratory findings of ongoing intra-abdominal hemorrhage but without other extra-abdominal or intra-abdominal injury precluding attempts at spleen preservation. In other words, these nine patients required laparotomy but either had an isolated spleen injury or other concomitant chest, head, extremity, or visceral injury not deemed of life-threatening proportions by the responsible surgeon. In each patient, an automated "cell-saver" (Haemonetics, Braintree, MA) was used at time of laparotomy, and the total volume of intra-abdominal blood reinfused in the nine patients was approximately 9000 mL (Table 1). One patient had concomitant cirrhosis of the liver (patient 5).

In five of the nine patients, preoperative abdominal computed tomography (CT) demonstrated not only a lacerated spleen but also considerable free blood both adjacent to the spleen and throughout the peritoneal cavity. The other four had physical findings of a rigid abdomen or evidence of ongoing hemorrhage (persistent hypotension, tachycardia, or diagnostic peritoneal aspiration yielding gross blood). Each patient had major parenchymal lacerations and in four, the laceration extended into the hilum (*i.e.*, grade III).[8] In two, a partial splenectomy was done, leaving a sizable remnant based on the two highest short gastric vessels (*i.e.*, the main splenic artery and vein were sacrificed); in three, splenic suturing was straightforward with omentum or Gelfoam (Upjohn, Kalamazoo, MI) inserted into the defect. In two others, however, splenorrhaphy was done by isolating the splenic pedicle, temporarily placing a lightweight vascular clamp on both the splenic artery and vein, and suturing the vessel "tear" via the laceration from within the spleen (Fig. 1). In two other patients, splenic repair was accomplished by circumferential coverage using an absorbable polyglycolic acid (Dexon; Kay Laboratories, Tulsa, OK) mesh, and one of these had delayed spleen necrosis necessitating later splenectomy (see below). In six patients, a postoperative scintiscan of the spleen or a splenic remnant also was carried out using autologous heat-damaged red blood cells, which provided both an image and quantification of "trapping" as an index of residual splenic function (Fig. 2).[9] In brief, autologous patient red blood cells were radiolabeled with technetium (99m sodium pertechnetate) and subsequently heat damaged by incubating for 30 minutes in a water bath preheated to 49.5 C. This technique reliably yielded more than 90% of incubated red blood cells labeled with radionuclide. After cooling, a sample was reinfused intravenously (5 mCi), and using a high-resolution collimator and gamma camera, scintiscans were done in the anterior and posterior projections. This method provided both a vivid biplanar image and quan-

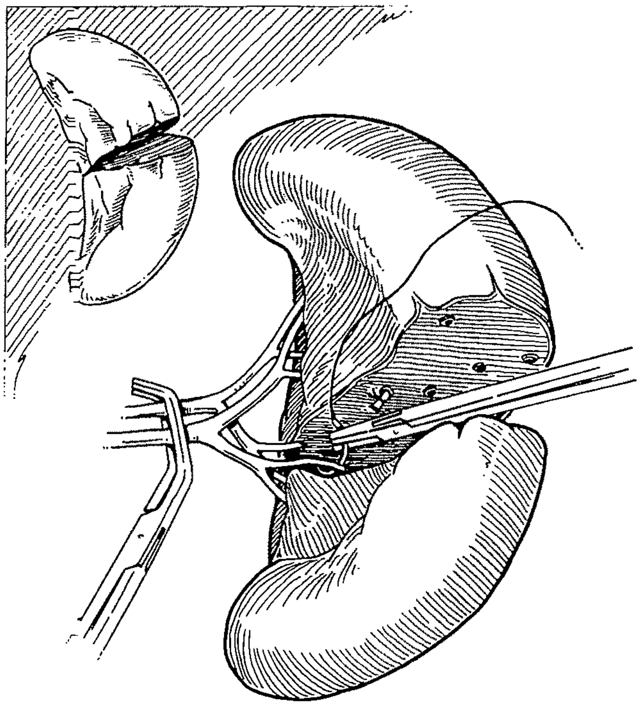

FIG. 1. Schematic diagram outlining a technique to manage splenic injuries in which lacerations extend into the hilum (*inset*). After the spleen is mobilized and the pedicle isolated, the splenic artery and vein are temporarily cross-clamped atraumatically. This maneuver renders the field bloodless and allows the torn polar branches to be sutured via the defect.

TABLE 1. *Clinical Summary of Nine Patients With Splenic Trauma Managed by Operative Preservation and Autotransfusion*

Patient	Sex	Age (yr)	Injury (grade)*	Salvage Procedure	Blood Loss (mL)	Autoinfused Blood (mL)	Exogenous Blood (mL)	Hematocrit (%) Admission	Hematocrit (%) Discharge
1	F	18	III	Partial splenectomy	>1500	500	0	42.0	29.3
2	M	16	II	Repair	>1500	1250	0	42.5	37.0
3	F	38	III	Repair	>2000	1250	0	41.1	28.3
4	M	8	II	Repair	>1000	500	0	22.2	20.0
5	M	35	II	Repair	>2000	1500	750	23.5	31.0
6	M	19	III	Partial splenectomy	>1500	750	0	41.8	34.0
7	F	35	III	Repair	>2000	1500	500	18.5	28.0
8	M	27	II	Repair†	>1000	1250	1000	32.2	25.7‡
9	F	52	II	Repair	>1000	500	0	38.3	35.0

* Grade II, deep parenchymal laceration(s); Grade III, hilar laceration(s).

† Spleen subsequently removed for infarction.

‡ Four days after operation.

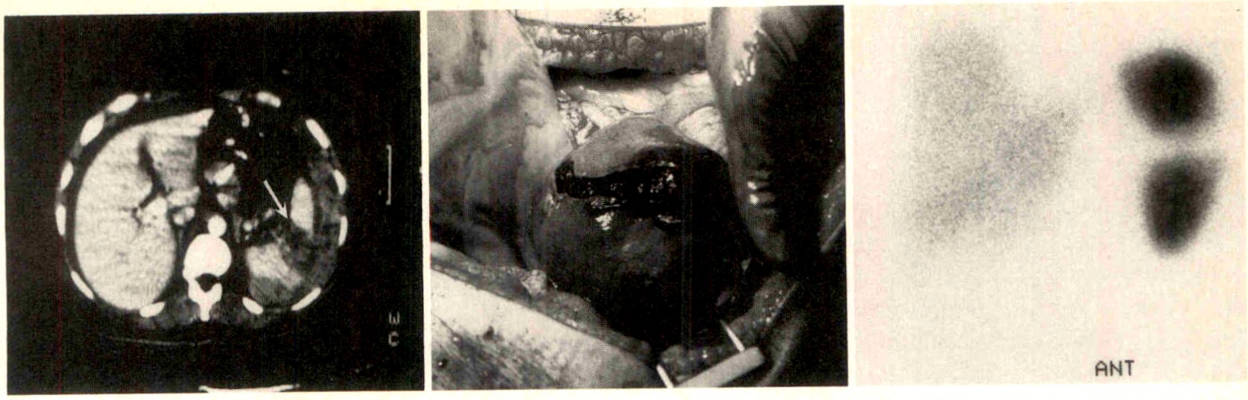

FIG. 2. A 38-year-old woman with isolated splenic injury after a motor vehicle accident. (Left) Abdominal computed tomography shows a disrupted spleen with the fracture extending into the hilum (*arrow*) and surrounding hematoma. (Center) At operation, a deep hilar splenic fracture with contained hematoma was encountered with more than 2000 mL of free and clotted blood in the peritoneal cavity. Using a cell saver, ~1250 mL of the autogenous blood was reinfused. With the technique described in Fig. 1, the polar branches were repaired and the splenic defect closed over mobilized omentum. (Right) A heat-damaged autologous red blood cell scintiscan 10 days later showed two large fragments with a normal trapping erythrocyte index of 40.8%.

tified blood-borne particle trapping, a key function of the spleen.[9] In three of the patients after splenorrhaphy (Table 1, patients 3, 4, 7), splenic red blood cell uptake was normal (43% ± 6%). Of the two patients with partial splenectomy, red cell uptake in one was 40.4% and in the other was 18.4%. The final patient with splenorrhaphy failed to show erythrocyte trapping, and subsequently an infarcted spleen was removed.

Discussion

The potential value of possessing a spleen and the feasibility of nonoperative management and repair if laparotomy is indicated for splenic injury is now generally accepted.[10,11] Nonetheless, a further reassessment is in order in view of the increasing risk of blood transfusion, ready availability of "red-cell savers" for reinfusion at time of laparotomy, and refined operative technique that makes spleen salvage increasingly likely except in avulsion or pulverizing injury.[3,10] Thus, children and even adults with isolated splenic injury are nowadays usually managed expectantly, including the use of blood transfusion.[12–14] Whereas a nonoperative approach is reasonable with hemodynamic stability, consideration of blood replacement should probably now dictate operative spleen salvage with reinfusion of shed intraperitoneal blood. The advantage to early operation is well demonstrated in six patients (Table 1, patients 1 through 4, 6, 9), in whom spleen sparing was accomplished without homologous blood replacement despite a mean intra-abdominal blood loss of approximately 1500 mL by successful autoinfusion of an average of 790 mL. Thus, the spleen or a large remnant was preserved, nonautologous blood transfusion was avoided, and prolonged "anxiety" regarding patient hemodynamic stability including the need for "round-the-clock" blood counts and critical-care monitoring was obviated. These principles apply to all nine patients, although, as shown in Table 1, in three (patients 5, 7, 8), besides 4250 mL autoinfused blood, another 2250 mL exogenous blood had to be administered.

Besides the distinct advantage of reducing or eliminating homologous blood transfusion, use of the "cell-saver" was also cost effective. We estimated that processing and administering just three units of homologous blood approximated the cost of "cell-saver" use for 4 hours, including the technician's services. Although the exact risk of transfusion-transmitted disease such as acquired immune deficiency syndrome (AIDS) and viral hepatitis is unknown, its incidence has been estimated as up to 7% per unit transfused.[15] Use of the "cell-saver," therefore, allowed spleen salvage to proceed safely and cost effectively, while sharply reducing the risk of transfusion-related complications.

In two patients with operative splenic repair and autotransfusion, the blood hematocrit rose to near-normal levels immediately after operation, only to decline sharply over the next 4 to 5 days. This hematocrit drop probably reflected membrane damage to the red blood cells traumatized from suction and rewashing, rendering them vulnerable to premature clearance by the salvaged spleen. Despite this occurrence, however, no further blood transfusions were required, and the autoinfused blood in conjunction with volume replacement by crystalloid solution was sufficient for hemodynamic stabilization during operative repair of the splenic injury.

The key to splenic repair or partial resection is, as others have suggested,[16] mobilization of the injured spleen by take-down of its ligamentous and short gastric attachments, as in preparation for total splenectomy. This maneuver has made repair of most major splenic injuries feasible with a variety of topical hemostatic agents, suture ligatures, and mesh techniques used for effective hemostasis.[3,10,11] Contrary to a recent review,[11] even patients with coexistent hepatic cirrhosis, as shown by patient 5, can be managed by splenorrhaphy. Lacerations that extend into the splenic hilum are more difficult, but with mobilization of the spleen, isolation of the splenic pedicle, and temporary arrest of afferent blood flow with a lightweight vascular clamp, the injury site can temporarily be rendered bloodless. After evacuation of intrasplenic hematoma by thorough irrigation with saline of the laceration defect, the hilum can be readily inspected and bleeding controlled by suturing from within the splenic parenchyma (Fig. 1). This technical approach is analogous to that described for retrohepatic injuries of the liver, where after cross-clamping the hepatoduodenal ligament (*i.e.*, portal vein and hepatic artery), the site of liver disruption is directly entered and torn hepatic venules sutured or "clipped" from within the hepatic parenchyma.[17] Where the splenic hilum is irreparably damaged, a sizable remnant often can still be retained (patients 1, 6).[9] "Trapping" by the remnant, moreover, can subsequently be examined by use of an autologous heat-damaged red cell scintiscan (Fig. 2), which provides a rough quantitative index of residual splenic function.[9] In four of the six patients examined postoperatively, residual spleen function was normal after repair or partial splenic resection. In another patient, trapping function was only ⅓ normal after partial splenectomy, but this residual spleen mass should suffice for protection against overwhelming sepsis.[18] In the final patient, failure to visualize the spleen corroborated necrosis and prompted early operation with removal of an "abscessed" spleen.

Although this report represents a small series, it is noteworthy that of the 20 consecutive patients injured in this 6-month period, only three required total splenectomy, two because of other life-jeopardizing injuries, and one

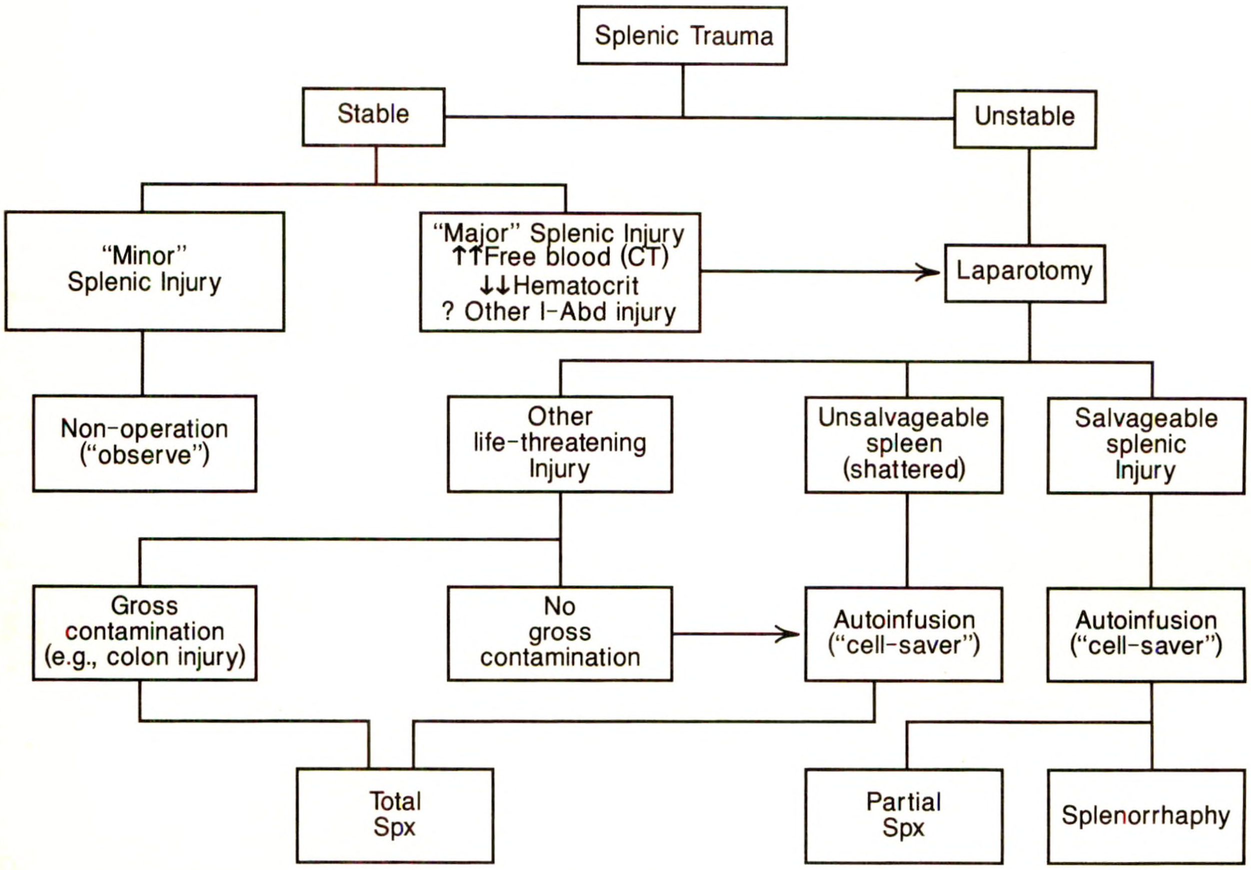
Splenic Trauma
Stable
Unstable
"Minor" Splenic Injury
"Major" Splenic Injury ↑↑Free blood (CT) ↓↓Hematocrit ? Other I-Abd injury
Laparotomy
Non-operation ("observe")
Other life-threatening Injury
Unsalvageable spleen (shattered)
Salvageable splenic Injury
Gross contamination (e.g., colon injury)
No gross contamination
Autoinfusion ("cell-saver")
Autoinfusion ("cell-saver")
Total Spx
Partial Spx
Splenorrhaphy

FIG. 3. Updated management plan for splenic trauma. With isolated splenic injury and hemodynamic stability, nonoperative management is appropriate. However, a large amount of free intraperitoneal blood, as seen on abdominal computed tomography, with a sharp drop in blood hematocrit and consideration for exogenous blood transfusion, or hemodynamic instability or concern over concomitant intraabdominal (I-Abd) visceral injury dictates prompt operation. Where the spleen is salvageable (*i.e.*, nonpulverized or no other contraindication to preservation), repair or partial resection is done in conjunction with a cell saver for reinfusion of autogenous shed blood. This approach saves the spleen or a sizable remnant and avoids homologous blood replacement with its risks of transmitting hepatitis or human immunodeficiency virus. Where spleen salvage is contraindicated (shattered spleen or other life-threatening injuries), total splenectomy is still warranted. Here, too, the cell saver reduces the need for homologous blood transfusion, although in certain injuries (*e.g.*, colon disruption) autoinfusion of massively contaminated blood is probably unwise. Spx, splenectomy.

as a complication of mesh encasement. In nine patients, the splenic injury was managed nonoperatively, and in eight, repair or partial splenectomy proved feasible for an operative salvage rate of 73% and an overall spleen salvage rate of 85%!

Based on this experience, we suggest updating the algorithm for management of splenic injuries (Fig. 3). Shattered spleens or concomitant life-threatening injuries still mandate total splenectomy. The availability of an automated cell salvage device with the capability of reinfusing large amounts of autologous blood at the time of laparotomy, thereby averting or sharply reducing the need for exogenous blood replacement, however, should significantly lower the threshold for early operation. In children, expectant therapy is still appropriate for splenic injuries unless other serious intra-abdominal trauma is suspected or bleeding continues. But if the need develops for blood transfusion, we now advocate operative spleen repair and autotransfusion of shed intra-abdominal blood using a "cell-saver" without other blood replacement. Similarly, in adults, unless splenic injury is a minor isolated phenomenon, we suggest early operation, spleen salvage, and reinfusion of shed autologous blood. This simplified approach avoids in both children and adults the danger of missing coexistent visceral injuries, largely circumvents the need for homologous blood replacement, obviates "round-the-clock" monitoring, and drastically reduces the cost of ancillary laboratory tests including serial blood counts and repeated abdominal CT scans. By saving the spleen (or a large remnant) and replacing circulating volume with autologous blood, management becomes optimal. Although one notable complication with eventual spleen loss occurred (patient 8) where a Dexon mesh wraparound was probably sutured too tightly, this modified approach to management of the injured spleen should not be associated with more short-term sequelae than total splenectomy or prolonged "watchful waiting" with homologous blood transfusion. Moreover, by minimizing the risk of blood-transmitted diseases such as viral hepatitis and AIDS, long-term complications should be reduced.

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Laser Doppler Flowmetry in Evaluation of Cutaneous Wound Blood Flow Using Various Suturing Techniques

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Measurements of blood flow on either sides of abdominal incisions and of uninjured control skin in 63 patients with three kinds of suturing techniques (clips in 21 patients, mattress in 21 patients, and subcuticular suture in 21 patients) on the 1st and 5th postoperative day were made, using an infrared laser Doppler flowmeter. There was a significantly higher flow on the 1st *versus* the 5th postoperative day. There is statistically higher blood flow in wounds sutured with subcuticular sutures in comparison with the two other groups. The method may allow the relationship of blood flow to wound healing to be evaluated.

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THERE HAS ALWAYS been a need to evaluate the blood flow to skin wounds in abdominal surgery, because it is well known that one of the main factors that may influence wound healing is the blood supply to the wound. An accurate measurement of this variable would aid immensely in the choice and evaluation of different suturing techniques or various kinds of sutures.

There have been many clinical and experimental studies on the effect of the choice of suture material on wound healing, in which no real differences were found.[1]

Other studies have implicated several patient-related factors (*e.g.*, advanced age, male sex, obesity, jaundice, diabetes, malnutrition, renal failure, malignant disease, corticosteroids) that allegedly increase the incidence of wound dehiscence.[2-8]

Except for improved nutritional status, these systemic factors cannot be altered by the surgeon, and their influence in wound healing seems unpredictable.[9]

Conversely, very little attention has been given to suture techniques in abdominal closure, which are factors that can be manipulated by the surgeon and may be of greater importance than patient-related factors.

In this clinical prospective study, we used a laser Doppler flowmeter (TSI Medical Instruments Group, St. Paul, MN) connected to a thermistor to evaluate blood flow on abdominal wounds closed with commonly used techniques of suturing: clips, mattress, and subcuticular sutures.

We used this atraumatic and well tolerated by the patient method to take measurements of blood flow on the 1st and 5th postoperative days, to assess any blood flow changes at the early stages of wound healing.

Instrumentation

The laser Doppler flowmeter (LDF) noninvasively measures capillary blood perfusion parameters, such as blood flow, velocity, and volume, in real time.

To measure these parameters, the probe head of the fiberoptic cable directs laser light (of a wavelength of 780 nm) into the tissue to a maximum depth of 1.5 mm, illuminating a volume of 1 mm^3, which contains both red blood cells and stationary tissue cells. Laser light is randomly scattered by both cell types. Photons scattered by moving cells are Doppler-shifted, and finally a portion of the scattered light is collected by multiple return fibers in the cable, which are coupled to a photodetector. There the light is converted into electronic signals to produce outputs directly proportional to blood flow.

A thermostatically controlled heated probe-holder (thermistor) that is connected to the LDF raises the tissue temperature to 45 C. Raising the temperature above normal eliminates changes due to environmental factors, and raising the local blood flow to near its theoretical maximum (through local vasodilatation) increases the sensitivity of this system.

Materials and Methods

We evaluated cutaneous blood flow in 63 consecutive patients (32 men and 31 women) ranging in age from 28 to 82 years, a median of 56 years, who had undergone abdominal surgery through three kinds of routine incisions

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(Kocher, right paramedian, and midline). Our material was divided into three groups of 21 patients, each according to the suturing technique used for abdominal closure: metallic clips (first group), mattress stitches (second group), and subcuticular suture (third group). On the first seven patients, for each kind of incision we used clips; on the following seven, we used mattress; and in the remaining seven, we used subcuticular suture. The particular suturing technique was selected on the basis of preference by the operating surgeon. The first seven patients for each incision and suturing technique were subjected to the cutaneous blood flow study. Because we were dealing with three different incisions and three different suturing techniques, this resulted in nine subgroups of seven patients each.

The median age for the three groups were 56 (range, 28 to 76) years in the first group, 59 (32 to 82) in the second group, and 54 (30 to 78) in the third.

All patients were operated on by the same surgical team, which followed the same technique as far as it concerns the skin closure. (The tension that was applied allowed for the skin edges to appose without tension, as far as it concerned the mattress technique).

The skin thermistor is circular in shape, with a radius of 0.6 cm. It carried the probe head of the fiberoptic cable exactly in its geometric center, so that the thermistor edge was applied right by the suture line, and the fiberoptic head of the LDF was taking measurements in a distance of 0.6 cm from the surgical incision.

The distance between the two consecutive stitches or clips, in which the measurements were done, was 1 cm.

Measurements on either sides of the wound edges and on the contralateral uninjured skin were done on the 1st and 5th postoperative days.

Blood pressure was taken before the onset of each measurement. None of the patients had pyrexia, and all of them were under antibiotics and prophylactic heparin administration (This is the policy of the clinic.).

The skin probe temperature throughout the procedure was 45 C, and the mean air temperature was 25 C.

The data were finally analyzed by the BBC Master microcomputer, which is connected to the LDF and appeared to the screen as a curve.

Results

The patients' data are summarized in Tables 1 and 2. We calculated the median values (and ranges) for all measurements in each group and compared them with the corresponding median blood flow on the 1st *versus* the 5th postoperative day ($p = 0.048$), which may indicate a generalized vasodilation in the first day after operation.

TABLE 1. *Median Blood Flow*

	Clips	Mattress	Subcuticular
Wound edges	3.1 (0.41–23.4)	3.7 (0.45–25.1)	6.2 (1.56–29.45)
Uninjured skin	5.4 (0.43–28)	5.2 (0.51–19.3)	5.6 (0.8–22.8)

First day after operation (mL/100 g/min).

TABLE 2. *Median Blood Flow*

	Clips	Mattress	Subcuticular
Wound edges	1.8 (0.9–10.5)	1.5 (0.3–19)	4.3 (1.0–30.5)
Uninjured skin	2.2 (0.27–24.4)	2.01 (0.22–27)	2.5 (0.2–24.9)

Fifth day after operation (mL/100 g/min).

There is also statistically higher flow in patients with subcuticular suture when compared with patients with clips and mattress in both the 1st and 5th postoperative days.

There are no statistically significant differences between the two other groups.

Discussion

For the three stages of wound healing—inflammation, proliferation, and maturation—to proceed normally, many factors such as energy expenditure, proper fluid and electrolyte balance, oxygenation, circulation, freedom from infection, and skilled surgical technique are required.

Inflammation, the first phase, is initiated at the time of injury and continues for 4 days. Hemostasis, phagocytosis, and cell migration occur in this phase. Proliferation, the second phase, is established by the 4th or 5th day after wounding and continues for 2 weeks. Activities in this phase include the proliferation of epithelial cells and fibroblasts, collagen synthesis, and an increased tensile strength of the uninjured tissues.

The third phase, maturation, begins in the second and third week after injury and may continue as long as 2 years.[4,3]

We took measurements of blood flow on abdominal wounds on the 1st and 5th postoperative days, so that we could evaluate any flow changes during the first two phases of the healing process.

The method that we present, laser Doppler flowmetry, has been widely used for measuring blood flow in various organs[10] and, compared with various other techniques such as fluorescein test,[11] xenon washout technique,[12] Doppler ankle pressure,[12] electromagnetic blood flow,[13] and venous occlusion plethysmography,[14] it has usually correlated well with them.

Furthermore, the method is relatively simple, rapid, requires a minimum of experience, is accurate, reproducible, noninvasive, well tolerated by the patient, and provides a continuous superficial measurement with a high-frequency response and relatively fine spatial resolution.[15]

The ability of laser Doppler flowmeter to analyze a very limited tissue volume has in experiments proven to be of great value in predicting successful healing of ulcerations and amputations of the ischemic forefoot. Other skin blood flow monitoring techniques have also clinically been used, such as Xe-133 isotope clearance technique in patients with peripheral vascular disease and with arterial insufficiency,[16,17] venous occlusion plethysmography in diabetes with neuropathic ulcerations,[8] Tc-33m washout technique in ischemic lesions of the lower limbs,[3] and distal ankle pressure in predicting healing of amputations.[17]

Revascularization is fundamental to the normal process of wound healing, and the rapidity of its onset and completion may be an index of the success of repair.

The effect of angiogenesis in wound healing may be the result of macrophages responding to tissue oxygen tension. An angiogenesis factor isolated from wound fluid stimulates the movement of capillary endothelial cells. It has been experimentally proven that an active angiogenesis factor is secreted by macrophages when they are found in the center of a wound, but when cultured under increasingly hypoxic conditions the macrophages begin to detach.[18,19]

Our measurements of blood flow on patients with three different techniques of abdominal closure show significantly higher blood flow values in wounds closed with subcuticular sutures. Although care was taken for the clips and mattress technique not to be tightly sutured, they constitute more massive techniques of skin closure when compared with a meticulously performed subcuticular suture. It seems that the more massive a closure technique is, the more it would cause ischemia of the tissues embraced by the sutures; as has been experimentally shown, 1 week after massive closure wounds exhibit a central zone of ischemia that resolves within 3 to 4 weeks with complete restoration of vascular anatomy.[20]

As far as the generalized vasodilatation measured on the 1st day, it is well known that the immediate response to wounding is vascular: there is a brief period of vasoconstriction affecting the vessels in the wound edges followed by vasodilatation and associated with the vasodilatation changes in capillary blood flow.

In conclusion, there is a statistically higher blood flow in wounds sutured with subcuticular technique in comparison with the two other groups.

Our findings suggest that the wound healing process might be more quickly initiated in this group of patients. Closing abdominal wounds with subcuticular suture may be a superior method of closure in clean incised wounds.

Our measurements with the LDF give valuable, comparative information on wound blood flow. One must constantly keep in mind that the healing process is regulated by multiple factors, and therefore the results could be unpredictable.

The method may allow evaluation of radiation therapy and chemotherapy or of the vasoactive agents on cutaneous wound blood flow, and should allow the relationship of blood flow to wound healing to be carefully studied.

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Comparison of Amputation With Limb-sparing Operations for Adult Soft Tissue Sarcoma of the Extremity

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The use of amputation in extremity soft tissue sarcoma has been decreasing at Memorial Sloan-Kettering Cancer Center (MSKCC) over the last 15 years. In an attempt to define the efficacy and future role of amputation in extremity soft tissue sarcoma, a prospective sarcoma database compiled at MSKCC from July 1982 to January 1990, consisting of 649 patients, was analyzed in a retrospective fashion. Ninety-two patients underwent amputation, and 557 had a limb-sparing procedure. Patients selected for amputation were those who had large ($T \geq 5$ cm) high-grade tumors that invaded major vascular or nervous structures. The amputation group achieved significantly better local control than the limb-sparing group ($p = 0.007$). No survival benefit could be demonstrated, however, in the groups selected for amputation (*i.e.*, large, high-grade tumors) when compared with patients undergoing a limb-sparing procedure with similar tumors. Prevention of local recurrence by amputation also did not improve survival in this group compared with similar patients undergoing limb-sparing surgery who did develop a local recurrence. The group of patients with high-grade tumors 10 cm or larger who received chemotherapy did have a significant improvement in survival ($p = 0.01$) compared with a similar group of patients who did not receive chemotherapy, regardless of the type of operation. The prognosis of patients most likely to undergo an amputation for extremity soft tissue sarcoma (those with high-grade, large tumors) is not related to their local disease, but rather to the risk of distant metastases. Therefore, amputation in this cohort of patients can be recommended only when a limb-sparing procedure cannot achieve gross resection of tumor while still preserving a useful extremity, because amputation improves only local control and does not address distant disease. Further improvement in survival in this group of patients will be dependent on better systemic treatment for extremity soft tissue sarcoma, and not on more radical surgery.

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VARIOUS AUTHORS HAVE determined the prognostic factors for survival in extremity soft tissue sarcoma. These factors include grade, size, depth, histology, distant metastases, lymph node metastases, and recurrence.[1-7] Decisions regarding surgical treatment as well as adjuvant radiation and chemotherapy have been based on these prognostic indicators.[8-14] Despite better definition of risk factors in this disease, however, tailoring of treatment to the individual patient based on these factors has been less well defined.[15,16] Surgical therapy for extremity soft tissue sarcoma at MSKCC has undergone a change in the last 15 to 20 years, with fewer amputations being performed in deference to limb-sparing procedures. From 1968 to 1978, 131 of 408 patients (32%) with extremity soft tissue sarcoma underwent amputation at Memorial Sloan-Kettering Cancer Center (MSKCC), compared with only 92 of 649 patients (14%) in 1982 to 1990 ($p = 0.05$).[10-17] This decrease in the incidence of amputations is most likely due to an improvement in local control secondary to external beam radiation therapy,[18,19] brachytherapy,[8,11-14,20-22] and doxorubicin-based (Adriamycin; Adria, Columbus, OH) chemotherapy regimens,[2,23,24] as well as a lack of evidence that amputation improved survival over limb-sparing procedures in patients considered for amputation.[1,9,17,25] As this evolution has taken place, however, the question of the efficacy and most appropriate role for amputation in extremity soft tissue sarcomas has remained unanswered.[8,26] We have attempted to answer these questions with this analysis.

Materials and Methods

A prospective sarcoma database established at MSKCC in July 1982 was analyzed in a retrospective fashion for the period of July 1982 to January 1990, with chart review, mailed questionnaire, or telephone contact used to update collected data. Type of therapy for each patient was determined by the individual surgeon based on alternatives and probability of local control and survival. Patients treated with chemotherapy received an Adriamycin-based

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regimen. Radiation therapy was delivered both by external beam and brachytherapy, as per the protocol established at MSKCC.[8,10–14,20,22] All patient tissue biopsies and tumor resections have been reviewed by a single pathologist. The database was analyzed with regard to which patients were most likely to be selected for amputation, and the results of this therapy were compared with those of limb-sparing surgery. As groups were identified as those most likely to undergo an amputation, further stratification and analysis specific for these groups was performed. Kaplan–Meier survival curves were generated, and the data were analyzed by log-rank analysis, chi square, and Fischer's exact test. Statistical significance was defined as $p < 0.05$.

Results

From July 1, 1982 to December 31, 1989, 649 patients with extremity soft tissue sarcoma underwent an operative procedure. For purpose of analysis, the patients were divided into two groups, those undergoing an amputation (n = 92) and those with a limb-sparing procedure (n = 557). Amputation was required as a salvage procedure in 18 of the 92 patients undergoing amputation during this period. Two of these eighteen patients undergoing amputation after limb-sparing surgery presented with local recurrence and metastatic disease simultaneously, whereas 14 of the 74 patients undergoing amputation for their primary tumor had metastatic disease at their presentation. Median follow-up for all patients was 22.7 months.

As shown in Table 1, age and sex were similar in the two groups. There were, however, significant differences among the groups with regard to grade, size of tumor, invasion of major nervous or vascular structure, and selection for chemotherapy. There were significantly more patients proportionally in the amputation group with high-grade tumors, tumors 5 cm or larger, or 10 cm or larger tumors invading a major nervous or vascular structure, and tumors requiring chemotherapy. Histologic differences were limited to significantly more patients with synovial sarcomas and chondrosarcomas in the amputation group and liposarcomas in the limb-sparing group. Because synovial sarcomas are usually located in joints and tend to invade bone, this may account for the increased incidence of these tumors in the amputation group. (In our series, 25 of 31 patients with synovial sarcomas that underwent amputation had their tumor located either in the foot or a joint.) Table 1 also points out the differences between the two groups with regard to site of tumors. Significantly more patients with tumors of the upper arm and thigh underwent limb-sparing procedures, whereas patients with tumors of the lower leg and foot were more likely to be treated with an amputation. Table 1 also demonstrates the number of each type of amputation performed over this period. Because patients with high-grade, large tumors were most likely to receive amputations, these groups were further analyzed to determine if these patients benefited from amputation.

TABLE 1. *Demographic Data for Patients Undergoing an Operation for Extremity Soft Tissue Sarcoma at MSKCC from 1982–1990*

	Amputation	Limb Sparing	
	(n = 92)	(n = 557)	
Age			
Range	17–88	17–92	
Mean	45	52	
Sex			
M	48 (52%)	290 (52%)	0.97
F	44 (48%)	267 (48%)	
Size (cm)			
Range	1–36	0.5–40	
Mean	10.6	8.7	
Median	9	5	
Tumor ≥ 5 cm	66 (79%)	307 (67%)	0.04
Tumor ≥ 10 cm	44 (53%)	167 (36%)	0.007
Grade			
High	79 (86%)	353 (64%)	0.00005
Low	13 (14%)	201 (36%)	
Major nerve/vessel invasion	10 (11%)	12 (2%)	0.000003
Chemotherapy	42 (46%)	141 (25%)	0.0001
Histology			
Synovial sarcoma	31 (34%)	54 (10%)	0.000003
Liposarcoma	6 (7%)	191 (34%)	0.000004
Leiomyosarcoma	6 (7%)	41 (7%)	0.2
MFH	11 (13%)	127 (23%)	0.07
Fibrosarcoma	5 (5.4%)	55 (10%)	0.06
Chondrosarcoma	6 (7%)	11 (2%)	0.02
MPNT	8 (10%)	30 (5%)	0.06
Rhabdomyosarcoma	1 (1%)	16 (3%)	0.2
Site			
Shoulder/axilla	4 (4.3%)	62 (11%)	0.07
Upper arm	3 (3%)	46 (8%)	0.04
Elbow	4 (4.3%)	10 (2%)	0.09
Forearm	5 (5.4%)	36 (6%)	0.2
Wrist	0 (0%)	1 (0.2%)	0.8
Hand	3 (3%)	9 (1%)	0.2
Finger	1 (1%)	1 (0.2%)	0.2
Buttock	1 (1%)	27 (5%)	0.06
Groin	2 (2%)	29 (5%)	0.1
Thigh	23 (25%)	245 (44%)	0.0009
Knee	6 (7%)	23 (4%)	0.1
Lower leg	14 (15%)	47 (8%)	0.06
Foot	15 (16%)	18 (3%)	0.000006
Ankle	1 (1%)	2 (0.3%)	0.3
Toe	3 (3%)	1 (0.2%)	0.009
Extent of amputation			
Hemipelvectomy	24 (26%)		
Hip disarticulation	6 (7%)		
Above knee	23 (25%)		
Below knee	13 (15%)		
Shoulder disarticulation	1 (1%)		
Forequarter	9 (10%)		
Above elbow	8 (9%)		
Digit	8 (9%)		

MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve tumor.

Survival curves for patients with tumors of at least 5 cm or at least 10 cm were generated (Figs. 1 and 2) to determine if patients with large tumors received a survival

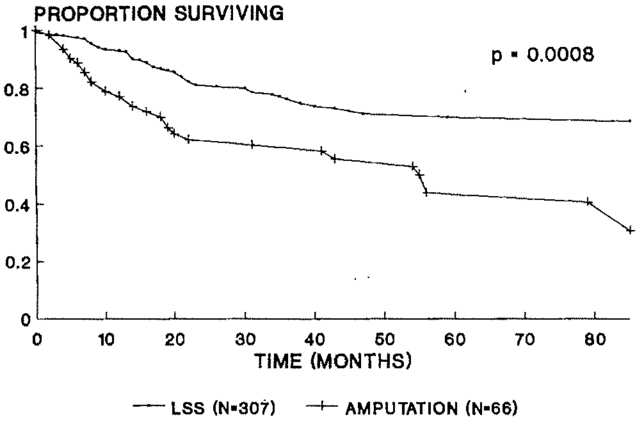

FIG. 1. Kaplan–Meier survival curves for patients who have tumors 5 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

benefit from their amputation compared with patients with similar-sized tumors undergoing limb-sparing surgery. From Figures 1 and 2, it is clear that amputation for large tumors did not improve survival. In fact, survival was significantly worse in the group of patients who underwent amputation for tumors 5 cm or larger or 10 cm or larger.

To explain this survival difference, this cohort of patients ($T \geq 5$ cm or $T \geq 10$ cm) was analyzed for grade of tumor. As shown in Table 2, patients with large tumors requiring an amputation had proportionally more high-grade lesions compared with patients undergoing limb-sparing procedures with large tumors ($p < 0.02$). This significant difference in grade among these two groups accounts for the significantly worse survival in the patients undergoing an amputation for tumors 5 cm or larger or 10 cm or larger.

The next factor that was significantly more predominant in the amputation group was high-grade lesions.

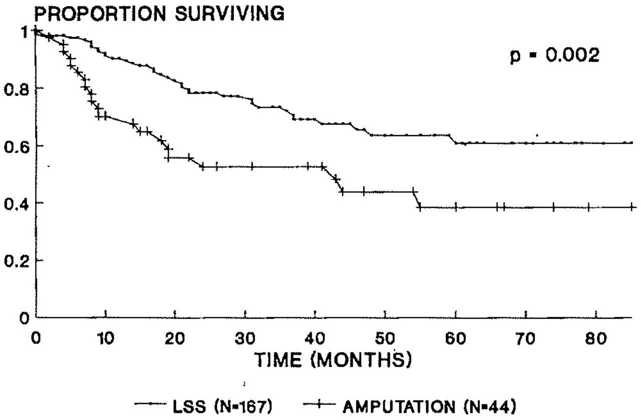

FIG. 2. Kaplan–Meier survival curves for patients who have tumors 10 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

TABLE 2. *Number of Large Tumors (≥5 cm or ≥10 cm) That are Also High Grade*

	Amputation (n = 92)	Limb Sparing (n = 557)	p
Tumor ≥ 5 cm, high grade	55/66 (83%)	208/307 (68%)	0.01
Tumor ≥ 10 cm, high grade	33/37 (89%)	61/86 (70%)	0.02

Survival curves again were generated for patients undergoing amputation *versus* limb-sparing surgery for high-grade lesions, and as can be seen in Figure 3, amputation did not improve survival. Survival was actually significantly better ($p = 0.001$) in the limb-sparing group compared with patients having an amputation.

This survival difference again can be accounted for by a difference in the two groups. There were significantly more tumors 10 cm or larger in the group with high-grade lesions requiring amputation (86%) compared with the limb-sparing group with high-grade lesions (64%), $p = 0.00005$.

To control for these differences between the two groups, the survival in patients with high-grade, large tumors undergoing amputation was compared with survival from limb-sparing surgery for similar lesions (Figs. 4 and 5). As before, there was no survival benefit for patients undergoing amputation for high-grade, large tumors.

The effect of amputation on survival in patients with low-grade, large lesions compared with limb-sparing surgery is shown in Figure 6. Again there is no survival advantage in this group of patients for amputation.

The question of local recurrence and its influence on survival is addressed in Table 3 and Figures 7, 8, 9, and 10. From Table 3 it can be seen that amputations resulted in significantly better local control ($p = 0.007$). Distant metastases, however, were more common in the ampu-

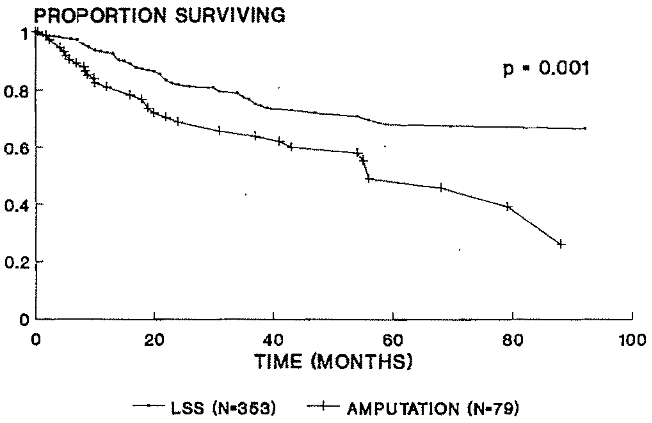

FIG. 3. Kaplan–Meier survival curves for patients who have high-grade tumors and who undergo limb-sparing surgery (LSS) *versus* amputation.

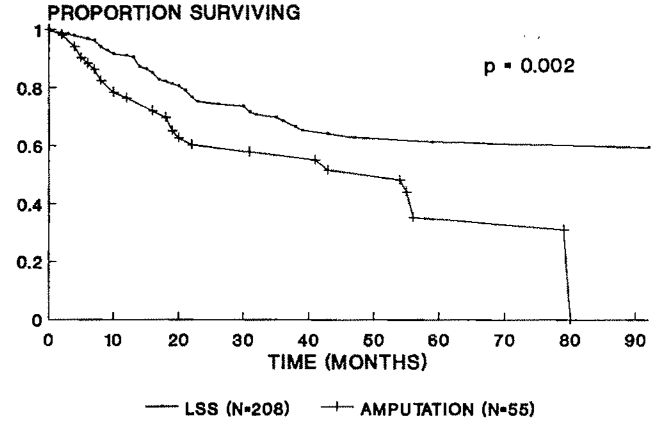

FIG. 4. Kaplan–Meier survival curves for patients who have high-grade tumors 5 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

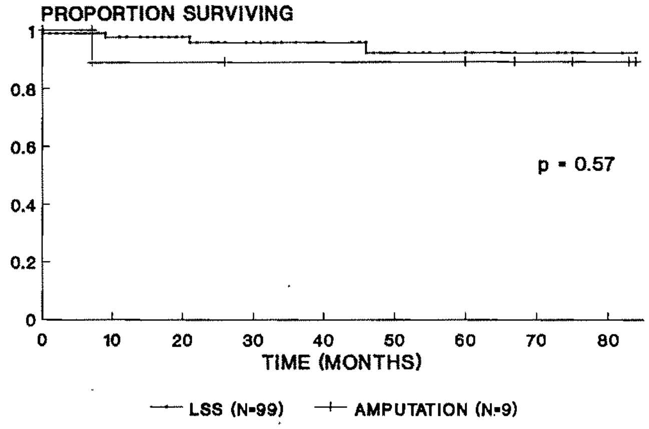

FIG. 6. Kaplan–Meier survival curves for patients with low-grade tumors 5 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

tation group compared with limb-sparing surgery (p = 0.000003), because they were more likely to have high-grade, large tumors, consistent with previous reports of high-grade tumors being associated with metastatic spread.[5,7,27,28]

The effect of local recurrence on survival can be seen in Figure 7, which compares survival in patients undergoing an amputation who do not develop local recurrence with those having a limb-sparing procedure who do develop local recurrence. Again, in the group of patients who underwent a limb-sparing procedure and developed a local recurrence, their survival was still better than the group with no local recurrence after an amputation.

Figures 8, 9, and 10 stratify the groups for grade (Fig. 8), large size (Fig. 9), and grade plus large size (Fig. 10), while again comparing the survival in patients undergoing an amputation who do not develop a local recurrence with patients undergoing a limb-sparing procedure who do develop a local recurrence. Despite stratifying for grade and size, there still is no survival advantage to achieving local control with an amputation in these cohorts of patients.

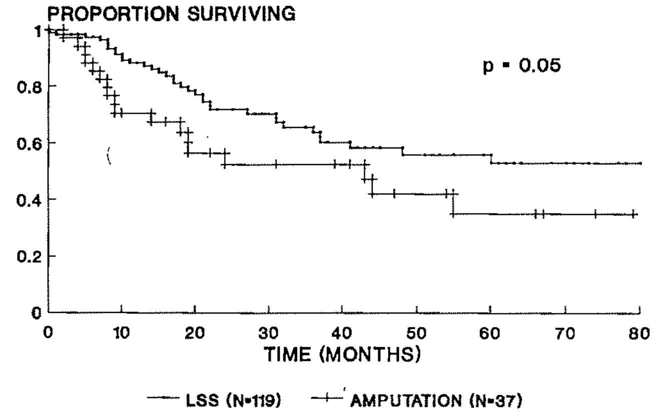

FIG. 5. Kaplan–Meier survival curves for patients who have high-grade tumors 10 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

Because better local control of the tumor in the amputation group did not lead to improved survival, the question of control of systemic disease with chemotherapy in this group is addressed in Figure 11. This figure compares the effect of chemotherapy on survival in all patients (undergoing either an amputation or limb-sparing surgery) with high-grade tumors 10 cm or larger. The survival in this group of patients who received chemotherapy was significantly better than in those patients not receiving chemotherapy, regardless of the type of operation.

Discussion

From the data presented, the patients selected to undergo an amputation for extremity soft tissue sarcoma at MSKCC from 1982 to 1990 were those thought to have the worst risk factors[1-7,9-14,27,29,30] (*i.e.,* high-grade, large tumors) and thus the worst prognosis. These patients were also more likely to receive chemotherapy. Based on the survival analysis for this cohort of patients (those with high-grade, large tumors), however, it is clear that these patients were not benefited from amputation as compared with limb-sparing procedures, despite stratifying the risk factors to make the groups as similar as possible.

TABLE 3. *Number of Patients Who Have Local and Distant Recurrences After Surgery*

Recurrence	Amputation (n = 92)	Limb Sparing (n = 557)	p
Local	6 (6%)	87 (15%)	0.007
Distant	36 (43%)	80 (14%)	0.000003
Total	42 (45%)	157 (28%)	0.001

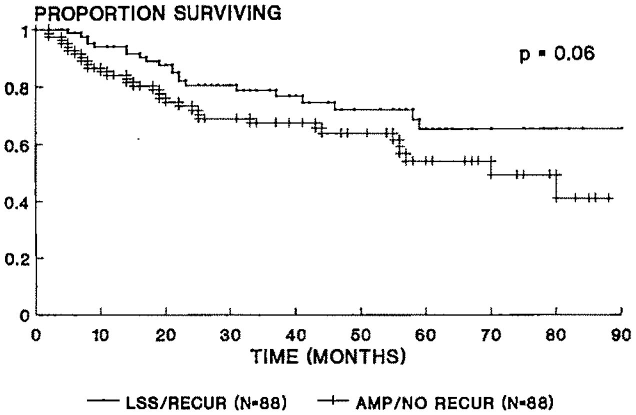

FIG. 7. Kaplan-Meier survival curves for patients who undergo a limb-sparing procedure (LSS) and who have a local recurrence (RECUR) *versus* patients who undergo amputation (AMP) and who do not have a local recurrence (NO RECUR).

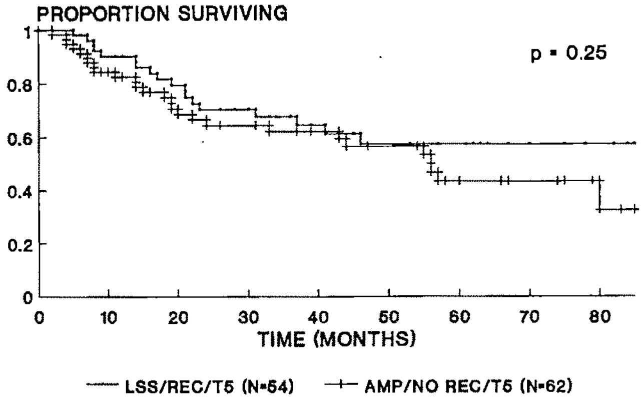

FIG. 9. Kaplan-Meier survival curves for patients who have tumors 5 cm or larger and who undergo a limb-sparing procedure (LSS) and have local recurrence (REC) *versus* patients who undergo amputation (AMP) for tumors 5 cm or larger and who do not have a local recurrence (NO REC).

Because any surgical procedure impacts only on the local disease, amputation proved significantly superior to limb-sparing surgery in local control and preventing locally recurrent disease.[25,26,31,32] Despite controlling the disease locally, however, amputation still did not improve survival over patients undergoing limb-sparing surgery in this series and others,[2,23,30] even if the patients undergoing limb-sparing surgery developed local recurrence and despite stratifying for risk factors. We and others have reported previously[9,17,27,33] that local recurrence did have a significant effect on survival in patients requiring an amputation for extremity soft tissue sarcoma. It is important to understand this apparent discrepancy of the effect local recurrence has on survival, because it points out the magnitude of the effect a lack of control of distant metastases has on this cohort of patients. In our previous report,[17] survival in patients undergoing amputation for extremity soft tissue sarcoma who developed a local recurrence was compared with patients with no recurrence (local or distant), leading to the apparent negative effect of local recurrence on survival. Figures 7 through 10, however, compare patients with limb-sparing surgery who develop a local recurrence only, with patients undergoing an amputation with no evidence of a local recurrence. These latter patients, however, may (and often did [Table 3]) still develop distant metastases. (Patients developing distant metastases in the study by Williard et al.[17] were censored for the analysis of local recurrence.) Explanation of this discrepancy highlights that survival in patients most likely to undergo an amputation (those with high-grade, large tumors) is dictated by the development of distant metastases and not by the development of a local recurrence. Thus, this apparent discrepancy points out the need for systemic control in these patients requiring amputation

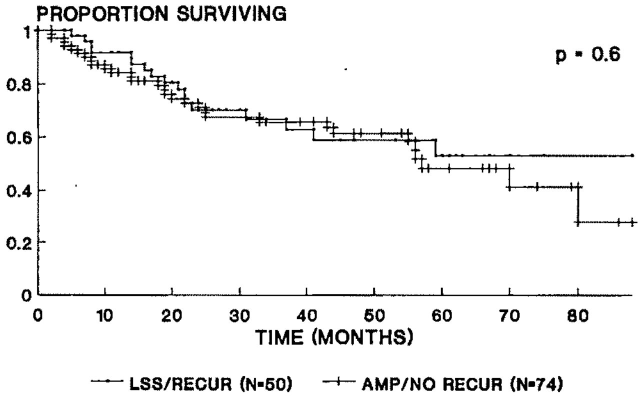

FIG. 8. Kaplan-Meier survival curves for patients who have high-grade lesions and who undergo a limb-sparing procedure (LSS) and have local recurrence (RECUR) *versus* patients who undergo amputation (AMP) for high-grade lesions and who do not have a local recurrence (NO RECUR).

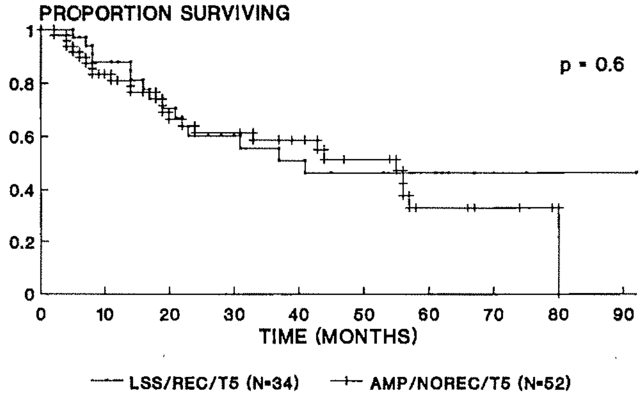

FIG. 10. Kaplan-Meier survival curves for patients with high-grade tumors 5 cm or larger who undergo limb-sparing surgery (LSS) and have local recurrence (REC) *versus* patients who undergo amputation for high-grade tumors 5 cm or larger and who do not have local recurrence (NO-REC).

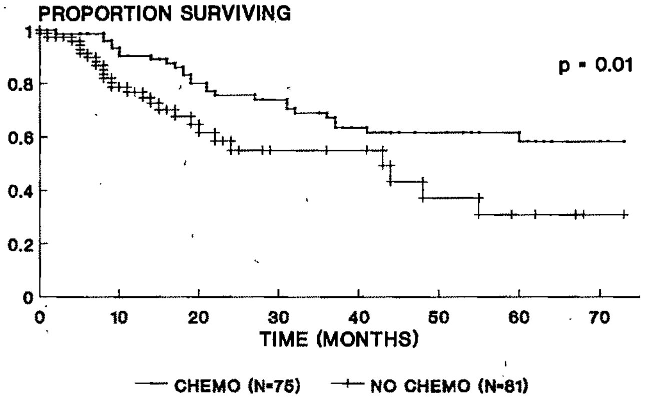

FIG. 11. Kaplan–Meier survival curves for patients who have high-grade tumors 10 cm or larger and who receive chemotherapy (CHEMO) *versus* patients who have high-grade tumors 10 cm or larger and who receive no chemotherapy (NO CHEMO) (amputation and limb-sparing groups are combined).

for extremity soft tissue sarcoma (because 43% of the amputation group developed distant metastases whereas only 6% developed a local recurrence [Table 3]), and shows local control to be of much less importance.

Another report by Emrich et al.[33] also stated that local recurrence significantly decreased survival in patients with high-grade extremity soft tissue sarcomas, with a 5-year survival rate of 44% in patients without a local recurrence *versus* 26% in patients who developed a local recurrence. Of the 184 patients who developed local recurrences in this study (a retrospective review), 141 had documented distant metastases. The authors cannot provide data regarding time of appearance of distant metastases in relation to the time of development of the local recurrence, but conclude: ". . . it is likely that a lack of local control of the tumor results in distant metastases, ultimately leading to a shorter survival time."[33] Again based on our data in Table 3, however, we would argue that most distant metastases arise from the primary tumor and are not secondary to a local recurrence that metastasizes. This conclusion is also supported by data from Huth and Eilber,[34] showing that development of a local recurrence—13 of 255 patients (5%)—was much less frequent than development of distant metastases—72 of 255 patients (28%)—among their patients with extremity soft tissue sarcoma. Heise et al.[7] reported similar results, with local recurrence in 100 of 594 patients (17%) *versus* 231 of 594 patients (39%) with distant metastases or simultaneous local recurrence and distant metastases. (We would propose that the simultaneous "detection" of local recurrence and distant metastases was from residual local microscopic disease as well as distant microscopic disease, present at the time of the initial resection and detectable only at a later date, because both cell populations increased in number at similar rates.) Thus, this would indicate that most patients with high-grade, large tumors requiring amputation already have systemic disease at the time of operation, and will not be benefited in terms of survival from a more radical procedure to control local disease.

The finding that the survival in patients receiving chemotherapy after resection of a high-grade tumor 10 cm or larger was significantly better than in those patients not receiving chemotherapy, regardless of the type of surgery, also lends support to the above premise. This observation is also supported by the only prospective, randomized trial reported in the literature,[23] with a recent update,[24] comparing limb-sparing surgery and adjuvant radiation therapy with amputation in patients with high-grade tumors, both groups being randomized to postoperative chemotherapy. The authors were able to show no survival advantage for amputation *versus* limb-sparing surgery in these patients with high-grade tumors, despite an increase in local recurrence in the limb-sparing surgery group. Also, patients receiving chemotherapy (doxorubicin, cyclophosphamide, and methotrexate) did have significantly improved survival regardless of their initial surgical procedure. Potter et al.,[2] with a similar patient population, reported similar data and conclusions. These findings support the concept of control of systemic disease as the primary predictor of outcome, with local control assuming a lesser role in these patients in terms of survival. Until better systemic therapy is developed to control distant disease, local control in extremity soft tissue sarcoma for high-grade, large lesions is not the issue.

One might reason that low-grade, large lesions, with a lower propensity for distant spread but with the difficulty in removing the entire tumor with clear margins with a limb-sparing procedure, would be better treated with an amputation. Our data suggest that these lesions are just as well treated by limb-sparing procedures, however, and that amputation does not offer a survival advantage in this group. This suggests that local recurrence, although morbid, can be dealt with by re-resection without increasing the mortality rate in patients with low-grade, large lesions. Again, multiple authors support this point, citing evidence that re-resection of local recurrences can render patients disease free and without worsening their prognosis.[2,3,34] Potter et al.[2] rendered seven of seven patients disease free after re-resection of a local recurrence, whereas Huth and Eilber[34] successfully re-resected 9 of 13 patients with local recurrence, with no subsequent evidence of systemic disease.

The role of amputation in extremity soft tissue sarcoma has been decreasing over the past 15 to 20 years. Clearly the groups this procedure is targeted at (those patients with high-grade, large lesions) have not obtained a survival benefit from this procedure. The prognosis of this cohort of patients is determined by their systemic disease (on which amputation obviously has no effect), and not their local tumor burden. The question of local recurrence leading to the development of distant disease is not definitively answered by this analysis, but the evidence supports that most patients considered for amputation (patients with large, high-grade tumors) will develop distant metastases from their primary tumor, without a local recurrence, and amputation of their extremity will not improve their survival. Because no group of patients could be demonstrated to obtain a survival advantage from amputation, we can only recommend this procedure for the patient whose tumor cannot be grossly resected with a limb-sparing procedure while still preserving a useful extremity. Further progress in the treatment of this disease awaits the development of more effective chemotherapeutic agents to address the systemic component of this disease. Until more effective systemic agents or other treatment modalities become available for these patients, the question of best local control will remain a secondary one, with equal or better survival being obtained with limb-sparing surgery when compared with amputation for patients with extremity soft tissue sarcoma.

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Blood Transfusion Impairs the Healing of Experimental Intestinal Anastomoses

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Blood transfusions are reported to impair the cell-mediated immune response. Because both T lymphocyte and macrophage function are important for wound repair, the authors investigated the effect of blood transfusions on anastomotic repair. Lewis rats underwent resection of both ileum and colon, followed by the construction of either an everted or an inverted end-to-end anastomosis. Immediately after operation, they received either 3 mL saline intravenously, or 3 mL heparinized blood from Lewis or Brown Norway donors. The animals were killed 3 or 7 days after operation, and anastomotic strength was assessed by measuring the bursting pressure. Anastomotic abscesses and generalized peritonitis were not found in the control group. Blood transfusions, particularly allogeneic, significantly increased the incidence of these septic complications. Three days after operation, anastomotic strength was significantly reduced in both Lewis and Brown Norway transfused groups. For instance, average bursting pressures (± standard deviation [SD]) of inverted ileal anastomoses were 79 ± 13 mmHg in the control group and 46 ± 14 and 21 ± 12 mmHg in the Lewis and Brown Norway transfused groups, respectively. Seven days after operation, the rupture site was found significantly more often within the anastomotic line in the animals that had received blood transfusions. The authors conclude that blood transfusions impair the healing of experimental intestinal anastomoses and increase susceptibility to intra-abdominal sepsis.

BLOOD TRANSFUSIONS HAVE been reported to alter the immune system. It has been known for some time that pretransplant transfusions prolong allograft survival.[1,2] Also, transfusions appear to enhance tumor growth in animal models, and to increase the recurrence rate of human colon, breast, and lung cancer.[3-7] Both experimental and clinical studies have demonstrated that blood transfusions increase susceptibility to septic complications.[8-11] Taken together, these studies suggest that blood transfusions may exert a generalized immunosuppressive effect.

Although the precise mechanism of this transfusion-induced immunosuppression has not yet been fully elucidated, there is evidence that blood transfusions impair the cell-mediated immune response.[12-14] Cell-mediated immune reactions depend primarily on two cell types, macrophages and T lymphocytes. Although the central role of macrophages in wound healing is well established, the possible importance of lymphocytes in this process has been recognized only recently.[15-18] With this evidence in hand, it seems logical to expect a detrimental effect of blood transfusions on the wound healing sequence. Anastomotic leakage is one of the major complications of gastrointestinal surgery and is often associated with high morbidity and mortality rates.[19,20] In a number of situations, for instance, in emergency operations, chances for anastomotic failure rise.[20,21] Blood transfusions have not been recognized as a potential risk factor for anastomotic leakage. Blood transfusions are frequently required in gastrointestinal surgery to correct anemia or because of excessive blood loss from associated trauma or operative procedures. Thus, it is important to establish the effect of such transfusions on intestinal repair. Because no data are as yet available on this subject, we conducted the present study in the rat, because we have gained considerable experience with such a model for anastomotic healing.[22]

Materials and Methods

Animals

One hundred twenty adult male Lewis rats, with an average weight of 235 ± 23 (± standard deviation [SD]) g were divided into two experimental groups of 60 rats each. An additional 20 Lewis male rats and 20 Brown Norway (BN) male rats were used as donor animals. All

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animals were kept in separate cages and were given food and water *ad libitum*. The animals were observed for a minimum of 1 week before initiation of the study to exclude the presence of any preexisting diseases.

Operative Procedure and Transfusions

The animals were anesthetized with intraperitoneal sodium pentobarbital and underwent a median laparotomy. One centimeter of both ileum and colon were resected at 15 cm proximal to the ileocecal junction and 3 cm proximal to the rectal-peritoneal reflection, respectively. In experiment I, everted one-layer end-to-end anastomoses were constructed microsurgically with 8 × 0 monofilament suture material (Ethicon). In experiment II, inverted anastomoses were used instead.

Blood was obtained from anesthetized Lewis and Brown Norway rats by cardiac puncture. The blood was heparinized and given through the dorsal penile vein. Within each experiment the animals were divided into three groups of 20 rats each, receiving 3 mL saline, 3 mL Lewis blood, or 3 mL Brown Norway blood, respectively. All transfusions were given immediately after the operation.

Investigations

Either 3 or 7 days after operation, the animals were anesthetized with intraperitoneal sodium pentobarbital. A second laparatomy was performed and the abdomen was inspected for the presence of abscesses and signs of generalized peritonitis. Both ileal and colonic anastomoses were prepared free, leaving surrounding tissue adherent to the anastomoses untouched, and removed. Thereafter, the animals were killed by an intraperitoneal overdose of sodium pentobarbital.

Approximately 5 cm intestinal segment containing the anastomosis was carefully cleaned from fecal content. Subsequently, the segment was attached to an infusion pump, filled with methylene-blue–stained saline solution. The pressure was increased with an infusion rate of 2.5 mL/min and recorded graphically. Both bursting pressure and site of rupture were noted.

In experiment II, the anastomotic segment was cleaned from surrounding tissue after the bursting pressure measurement, and a 0.5 cm segment, containing the anastomosis, was collected for analysis. The samples were frozen immediately and stored in liquid nitrogen until processing. After weighing, the samples were pulverized and lyophilized, and the hydroxyproline content was measured as described before.[23]

Statistical Analysis

Statistical methods are given with the results.

Results

Experiment I

Body Weight. All animals showed weight loss in the early postoperative period, followed by some weight gain later on. Average weight loss (± SD) on the third day postoperatively in the saline, Lewis, and Brown Norway transfused groups was 18.2 ± 4.6 g (n = 8), 19.4 ± 5.3 g (n = 7), and 25.6 ± 6.7 g (n = 8), respectively. Average weight gain with respect to weight at operation on the seventh day after operation in the three groups was 11.7 ± 10.6 g (n = 10), 8.4 ± 7.6 g (n = 7), and 6.3 ± 11.5 g (n = 10), respectively. The differences between groups were not statistically significant (Kruskal–Wallis test).

Mortality Rate. In the groups receiving saline or Brown Norway blood, the postoperative mortality rate was 10%, whereas animals transfused with Lewis blood exhibited a mortality rate of 30%. Two animals in the saline group died between the first and the second postoperative days, without any macroscopic evidence of anastomotic leakage or intra-abdominal infection. One rat showed signs of ileus. Animals transfused with Brown Norway blood or Lewis blood died between the second and the fourth days after operation. All of these exhibited signs of intra-abdominal sepsis, such as anastomotic abscesses or generalized peritonitis.

Intra-abdominal Sepsis. No abscesses were found at all around the anastomoses in the saline-infused group. On the contrary, high numbers of anastomotic abscesses were found after blood transfusions (Table 1). On the third day after operation, abscesses were found around 57% of the ileal anastomoses in the Lewis group, and around all anastomoses constructed in rats transfused with Brown Norway blood. A similar, although less explicit, effect was observed in colon. Next to the anastomotic abscesses, signs of generalized peritonitis and fascial abscesses were found also in 29% of the Lewis group, and 50% of the Brown

TABLE 1. *Anastomotic Abscesses and Bursting Pressures in Experiment I*

	Day 3			Day 7		
	n	Ileum	Colon	n	Ileum	Colon
Abscess						
Saline	8	0	0	10	0	0
Lewis	7	4	2	7	2	2
Brown Norway	8	8	4	10	4	2
p		0	0.07		0.08	NS
Bursting pressure						
Saline	8	31 ± 3	45 ± 11	10	325 ± 38	270 ± 23
Lewis	7	14 ± 3	32 ± 5	7	238 ± 31	166 ± 24
Brown Norway	8	13 ± 4	23 ± 9	10	207 ± 26	182 ± 26
p		0.0005	0.001		0.0001	0.0001

Bursting pressures are expressed as average (mmHg) ± SD. Differences between groups were tested for significance with a Kruskal–Wallis test.

Norway group. No such complications occurred in the saline group. Seven days after operation, abscesses still could be observed around ileal anastomoses in 29% of the animals in the Lewis group and in 40% of those in the Brown Norway group. This phenomenon was seen also around colonic anastomoses. In addition, 20% of the rats transfused with Brown Norway blood showed signs of generalized peritonitis.

Bursting Pressure and Bursting Site. The strength of the anastomoses, as assessed by the bursting pressure, was significantly impaired after blood transfusions (Table 1, Fig. 1). Three days after operation, the bursting pressure of both ileal and colonic anastomoses in the Lewis and Brown Norway transfused groups was significantly reduced as compared with the saline group. At this point, all anastomoses ruptured within the suture line. At 7 days postoperatively, similar, statistically highly significant differences were observed between the three groups. At this time, however, the bursting pressure in the saline group does not reflect anastomotic strength, because the bursting site was always outside the anastomotic area. Thus, the actual average anastomotic strength must have been even higher than the figure given in Table 1. Moreover, in the ileum of the Lewis group, rupture occurred within the anastomosis in two of seven cases. In the Brown Norway group, this happened in seven of 10 anastomoses. This constituted a statistically significant (p = 0.004, chi square test) shift in bursting site between groups. A similar, although statistically not significant, phenomenon was observed with regard to the colonic anastomoses (Fig. 1). Finally, it should be noted (Fig. 1) that anastomoses with abscesses always ruptured at the suture line—also at 7 days—and that their strength was always lower than that of the anastomoses without abscesses.

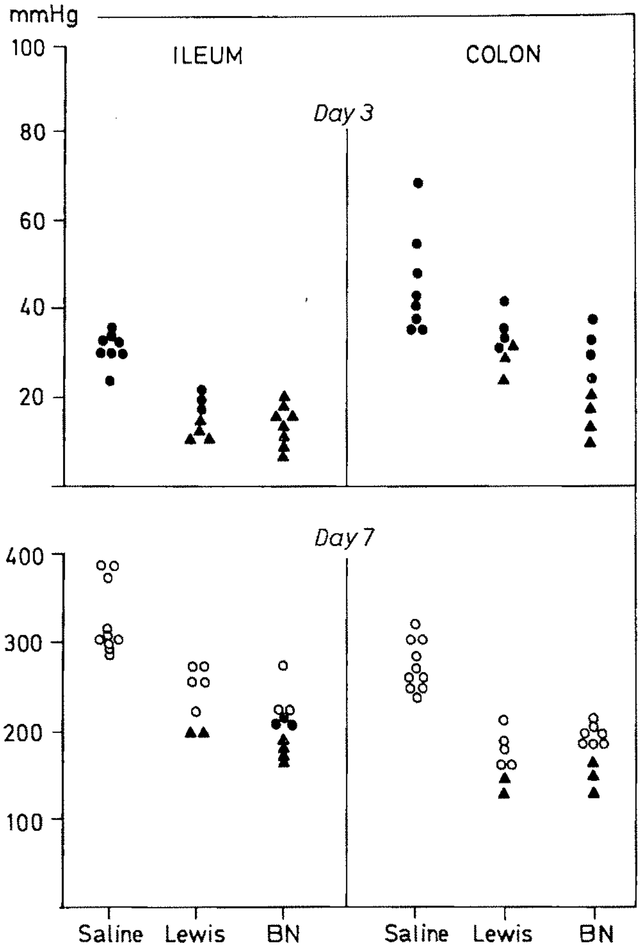

FIG. 1. Correlation between bursting pressure, bursting site, and anastomotic abscesses in experiment I. Points represent single anastomoses. Closed symbols, rupture within suture line; open symbols, rupture outside suture line; circles, no anastomotic abscess; triangles, anastomotic abscess present.

Experiment II

The results of experiment II, where inverted anastomoses were constructed instead of everted anastomoses, were similar to those of experiment I.

Body Weight. The average weight loss (±SD) on the third postoperative day was 18 ± 6 g (n = 10) in the saline group, 19 ± 4 g (n = 9) in the Lewis group, and 20 ± 6 g (n = 8) in the Brown Norway group. Seven days after the operation, all animals had gained some extra weight, with respect to their preoperative weight. The average increase (±SD) was 16 ± 12 g (n = 10) in the saline group, 8 ± 4 g (n = 8) in the Lewis group, and 6 ± 9 g (n = 10) in the Brown Norway group. Differences between groups were only significant at day 7 (p = 0.04, Kruskal-Wallis test).

Mortality Rate. The postoperative mortality rate appeared higher after blood transfusions. The mortality rate was 15% in the Lewis transfused group and 10% in the group transfused with Brown Norway blood. The animals died between the second and the third day after operation, exhibiting intra-abdominal septic complications. None of the animals receiving saline died before being killed.

Intra-abdominal Sepsis. Again, animals that received saline formed no abscesses at all around the anastomoses. At both 3 and 7 days after operation, an increased occurrence rate of abscesses was observed around the ileal anastomoses in both transfusion groups. This effect was more pronounced after transfusion with allogeneic—Brown Norway—blood (Table 2). In the colon, anastomotic abscesses were seen only twice 3 days postoperatively. After 7 days, however, they were found in four of eight animals transfused with Lewis blood and in six of 10 animals transfused with Brown Norway blood.

Generalized peritonitis and abdominal wall abscesses were only observed in the Brown Norway group, in 25% and 50% of the animals at 3 and 7 days after operation, respectively.

TABLE 2. *Anastomotic Abscesses and Bursting Pressures in Experiment II*

	Day 3			Day 7		
	n	Ileum	Colon	n	Ileum	Colon
Abscess						
Saline	10	0	0	10	0	0
Lewis	9	2	0	8	1	4
Brown Norway	8	7	2	10	6	6
p		0	0.07		0.005	0.01
Bursting pressure						
Saline	10	79 ± 13	97 ± 19	10	303 ± 50	241 ± 17
Lewis	9	46 ± 14	66 ± 9	8	254 ± 47	191 ± 35
Brown Norway	8	21 ± 12	47 ± 12	10	198 ± 56	183 ± 28
p		0	0		0.001	0.001

Bursting pressures are expressed as average (mmHg) ± SD. Differences between groups were tested for significance with a Kruskal–Wallis test.

Bursting Pressure and Bursting Site. The strength of the inverted anastomoses (Table 2) in the saline group was higher than the strength of the everted anastomoses (Table 1). Transfusions again induced significant loss of strength, however, both 3 and 7 days after operation. Two-by-two comparison of the experimental groups also showed that the bursting pressures of 3-day-old anastomoses were significantly lower in the Brown Norway transfused group than in the Lewis transfused group (p = 0.005 in ileum and p = 0.007 in colon, Wilcoxon one-sided test).

As in the first experiment, all 7-day-old anastomoses in the saline group were stronger than the adjacent bowel wall. In the ileum of the Lewis and Brown Norway transfused groups, rupture occurred within the suture line in 12.5% and 70% of the cases, respectively (p = 0.001, chi square test). For colon, these values were 50% and 60%, respectively (p = 0.01, chi square test). Figure 2 shows that again anastomoses with abscesses invariably ruptured within the wound area and yielded much lower bursting pressures than those healing in a peritoneal cavity without signs of infection.

Hydroxyproline Content. The hydroxyproline content is taken to be a measure for the anastomotic collagen level. Three days after operation, the hydroxyproline content of the colonic anastomoses was significantly lower in the transfusion groups than in the saline group. In the ileal anastomoses, this effect remained nonsignificant. No differences between groups were observed 7 days postoperatively, either in ileum or in colon (Table 3).

Discussion

After the discovery of the ABO groups by Landsteiner in 1900, blood transfusions have become a common treatment for correction of anemias and for the replacement of significant losses as a result of trauma of operation. During the last decade, however, increasing evidence has emerged that blood transfusions carry certain risks, previously unrecognized, for the patient, in particular with respect to immunosuppression. These include diminished cell-mediated immune response, decreased helper/sup-

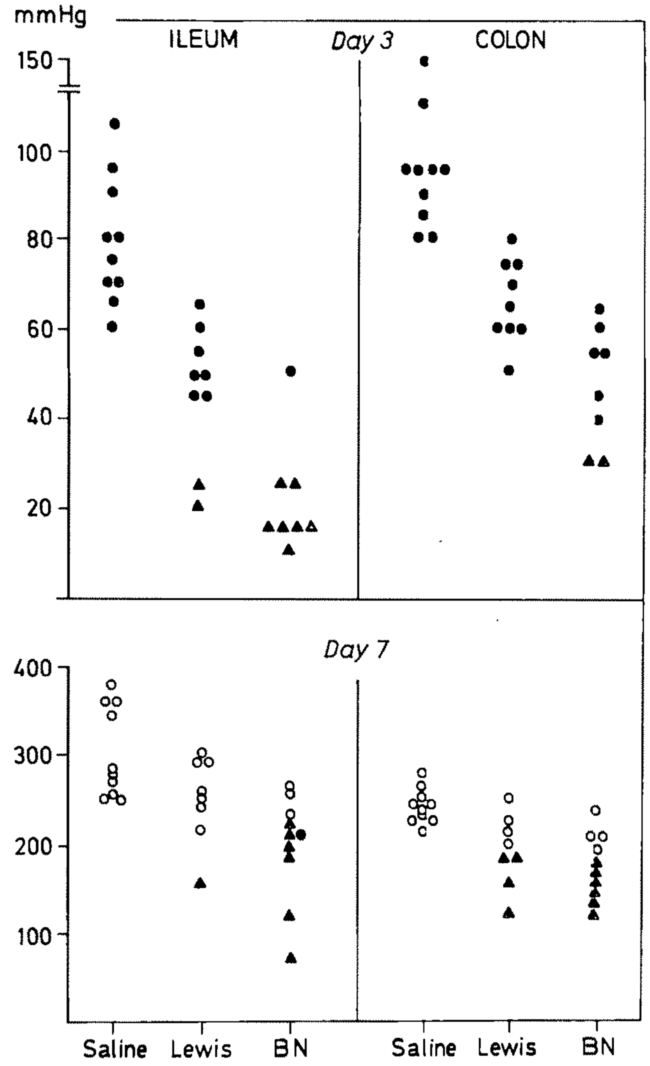

FIG. 2. Correlation between bursting pressure, bursting site, and anastomotic abscesses in experiment II. Points represent single anastomoses. Closed symbols, rupture within suture line; open symbols, rupture outside suture line; circles, no anastomotic abscess; triangles, anastomotic abscess present.

TABLE 3. *Anastomotic Hydroxyproline Content in Experiment II*

	Day 3			Day 7		
	n	Ileum	Colon	n	Ileum	Colon
Saline	10	90 ± 12	176 ± 27	10	164 ± 29	244 ± 48
Lewis	9	80 ± 19	122 ± 30	8	167 ± 25	270 ± 39
Brown Norway	8	79 ± 29	121 ± 27	10	169 ± 36	301 ± 75
p		NS	0.003		NS	NS

pressor T-cell ratios, decreased natural killer cell activity, suppression of lymphocyte blastogenesis, and decreased macrophage antigen presentation.[12-14,24-26] Recently, a role has been recognized for immune regulatory cells in the wound healing process. Activated lymphocytes have been shown to secrete lymphokines, which *in vitro* alter fibroblast replication, migration, and collagen synthesis.[18] Impairment of skin wound healing was observed after *in vivo* depletion of T lymphocytes.[16] Thus, it seems likely that blood transfusions will affect the healing process. We have investigated anastomotic healing in the intestine because blood transfusions are frequently required in both elective and emergency gastrointestinal surgery, and failure of intestinal repair is a most serious complication with high morbidity and mortality rates.

To compare the effects of both syngeneic and allogeneic blood, two rat strains have been used as donors. Human transfusions are crossmatched for blood groups, but not for histocompatibility antigen mismatches. In an attempt to approach this situation, we chose the Brown Norway rat as a donor and the Lewis rat as a recipient. No hemolysis occurs in this transfusion model, but there exist histocompatibility differences, which approximate those in human transfusions.[27] In an effort to establish the consistency of the results, we performed two separate experiments using different types of anastomoses. Furthermore, no blood was taken before operation, to avoid possible effects of hemorrhage. The results of this study clearly demonstrate that blood transfusions impair the healing of intestinal anastomoses. The strength of both ileal and colonic anastomoses was significantly decreased in those rats that received either allogeneic or syngeneic blood, at both time points measured. The impairment of healing was most explicit in the allogeneically transfused rats (Brown Norway group).

Allogeneic and syngeneic blood transfusions caused an increase in the occurrence rates of anastomotic abscesses, fascial abscesses, and peritonitis. Most of the abscesses were found on the third day after operation. The morbidity rates were higher in the rats transfused with allogeneic blood than in those transfused with syngeneic blood, whereas none of the animals that received saline showed any signs of intra-abdominal sepsis. Figures 1 and 2 clearly demonstrate that the presence of anastomotic abscesses correlates with reduced anastomotic strength. These data thus confirm an increased susceptibility to septic complications after syngeneic and, particularly, allogeneic blood transfusions.

Two lines of reasoning could explain our results: blood transfusions either affect healing directly or induce intraperitoneal infections, which in turn affect healing.

In the first case, transfusions would interfere with the cellular phase of the inflammatory reaction. The role of macrophages in wound healing is well known. Macrophages release a number of cytokines and growth factors, which stimulate fibroblast proliferation (and thereby synthesis of collagen) and neovascularization.[28]

Waymack et al.[12] have demonstrated a significant impairment in the migration of macrophages into the peritoneal cavity in response to inflammatory stimuli in allogeneically transfused rats. Also, macrophages obtained from allogeneically transfused rats were found to have significant alterations in their arachidonic acid metabolism, including an increase in the production of thromboxane, prostacyclin, and prostaglandin E.[29,30] Thus, the impairment of healing could be due to alterations in macrophage migration and function. Leakage, and subsequent abscess formation, could occur as a result of inadequate development of bowel wall strength.

Another cell that appears to be involved in the wound healing process is the T lymphocyte. Although *in vivo* depletion of T lymphocytes resulted in impaired wound healing,[16] depletion of T-helper/effector cells had no effect on wound healing, and depletion of the T-suppressor/cytotoxic subset even enhanced healing.[17] Conversely, blood transfusions have been shown to diminish lymphocyte blastogenesis in response to mitogen stimulation and to increase suppressor cell activity.[24,25] In addition, blood transfusions exert a negative influence on the generation of interleukin-2,[26,31] which compound has been reported to enhance wound healing in rats.[32]

A second line of reasoning would be that blood transfusions primarily cause intraperitoneal infection, which then affects the healing of intestinal anastomoses. Tartter et al.[8] reported increased rates of infectious complications after colon surgery in patients given blood transfusions in the perioperative period. The presence of peritonitis or abscesses has been known to result in increased leakage and reduced strength of intestinal anastomoses.[20,33] Waymack et al.[10] reported decreased resistance to *Escherichia coli* peritonitis challenges, and impaired macrophage bactericidal function[34] in allogeneically transfused rats.

The higher incidence of abscesses around ileal anastomoses as compared with colonic anastomoses, however, might argue against the second explanation. If transfusions impaired healing primarily because of induction of intraperitoneal infection, more anastomotic abscesses should have been found in colon than in ileum, because of the lower concentration of microorganisms in ileum.

It should be noted that, although differences were found between groups with regard to the average hydroxyproline content of anastomoses, these reached significance only in colon (on day 3). Also, at 7 days after operation, the average anastomotic hydroxyproline content in the colons of animals transfused with either Lewis or Brown Norway blood tended to be higher in comparison with the saline group. These findings suggest that blood transfusions not so much affect the quantity of the anastomotic collagen, but possibly even more its quality, which might very well decide eventual anastomotic strength.

At this time, it remains unexplained why syngeneic blood also suppresses the healing of intestinal anastomoses. This finding is similar to results of other studies, however. Waymack et al. also found that syngeneic transfusions increase susceptibility to infections,[9,29] and impair lymphocyte blastogenesis.[25] One possible explanation would be that the animals in the syngeneic group, although littermates of the recipients, were not identical twins. This phenomenon could also mean that there are other—as yet unknown—factors that may contribute to the effect of blood transfusions on wound healing.

In conclusion, the present data clearly demonstrate that—in our model—blood transfusions impair the healing of intestinal anastomoses, and increase susceptibility to intra-abdominal septic complications, possibly as the result of an alteration of the local or systemic immune response to the traumatic injury of the intestine caused by the surgical procedure. Further research in this area is certainly required because of the possible clinical consequences of these findings.

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The Effect of Tumor Bulk on the Metabolic Response to Cancer

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The derangements in energy/substrate metabolism seen in oncology patients are similar regardless of the tumor's site of origin, and in advanced disease these metabolic derangements can be manifested as cancer cachexia. The relationship between tumor size and the degree of metabolic abnormality, however, remains unclear. Using primed constant infusions of stable and radiolabeled isotopes and indirect calorimetry, the authors have determined the rates of net protein catabolism (NPC), glucose oxidation, Cori cycling of glucose, and oxygen consumption in 85 patients with cancer. They have assessed the association between bulk of tumor and metabolic abnormality using regression analysis. A positive correlation was found between tumor bulk and the rates of NPC ($r^2 = 0.8$), plasma glucose appearance ($r^2 = 0.72$), plasma glucose clearance ($r^2 = 0.70$), the percentage of tissue glucose uptake recycled to lactate ($r^2 = 0.62$), and oxygen consumption ($r^2 = 0.79$). The percentage of tissue glucose uptake oxidized was negatively correlated with tumor bulk ($r^2 = 0.75$). The data indicate that the degree of metabolic abnormality seen in cancer patients is closely related to the quantity of malignant tissue present. Progressive increase in tumor size is associated with an increase in peripheral substrate mobilization, an increase in the rate of hepatic glucose production, an increase in tissue glucose uptake, an increase in energy-expensive glucose cycling to lactate, and an increase in protein loss.

IT IS NOW clear that tumor burden is associated with abnormal energy substrate metabolism in the host.[1-3] In spite of this, the relationship between the stage of disease or bulk of tumor present and the development of abnormal energy/substrate metabolism is unclear. Cancer cachexia is more common in advanced tumors, and weight loss is a sign of heavy tumor burden.[4] There are, however, a number of reports in the oncology literature of significant weight loss in association with relatively small tumor burdens.[5,6]

We have previously shown that patients with small or early tumors are metabolically similar to postabsorptive cancer-free volunteers,[1] whereas patients with more advanced or aggressive tumors exhibit a number of metabolic abnormalities that eventually may present as cancer cachexia.[1,7,8] In addition, we and others have previously shown a remarkable similarity in the metabolic derangements that accompany cancer regardless of the primary site or tissue of origin,[1-3,7,8] and it has been postulated that the elaboration of endocrine mediators by rapidly growing malignant tissue alters host metabolism in a way that is more advantageous to tumor growth.[3,9,10]

This study of metabolic profiles in cancer patients was undertaken to define the relationship between the bulk of tumor and the common metabolic abnormalities associated with tumor burden.

Methods

Patients

All patients in this investigation were recruited from the general surgical wards at Auckland Hospital. This investigation was approved by the Ethical Committee at Auckland Hospital, and the use of radioisotopes was approved by the National Radiation Laboratory of New Zealand. Many of the metabolic data from these patients have been published previously in a number of investigations concerning the metabolic profile of individual malignancies.[1,7,8] We have not previously investigated the association between the bulk of tumor and the metabolic response to tumor burden, however. We therefore reviewed the results of 5 years of isotopic studies in cancer patients and selected all oncology patients who were studied preoperatively. No oncology patient was included in this analysis if they had significant sepsis, concurrent en-

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docrine disease (including diabetes mellitus), or if they were receiving total parenteral nutrition. The majority of patients studied were suffering from solid tumors of the gastrointestinal tract, retroperitoneum, or limbs. The patients with myeloproliferative cancers who were studied all had disseminated disease and were referred to the surgical service for staging laparotomy or splenectomy.

The clinical details of the 85 patients are presented in Table 1.

Measurement of Tumor Bulk

The pathologic records of the patients who had solid tumors removed after metabolic study were reviewed, and the dimensions of tumor in the resected specimen made by an independent pathologist were noted. It was assumed that solid tumors were uniformly spherical in shape, and the volume of tumor present was calculated using these dimensions. It also was assumed that 1 cm^3 of tumor tissue weighed 1 g. No attempt was made to subtract the dimensions of any necrotic tumor segments from this value. The volumes and weights of any hepatic or pulmonary metastases were calculated in the same manner using the dimensions obtained with ultrasound or computed tomographic (CT) scanning.

In those patients with myeloproliferative cancers, it was assumed that all hemopoietic tissue (excluding the spleen) was uniformly malignant and the volume of this was cal-

TABLE 1. *Clinical Details of Oncology Patients*

Patient	Sex	Age	Diagnosis	Patient	Sex	Age	Diagnosis
1	M	64	Ca esophagus	44	M	67	Ca colon
2	F	80	Ca pancreas	45	F	72	Ca rectum
3	M	64	Ca stomach	46	F	69	Melanoma
4	M	87	Ca esophagus	47	F	58	Melanoma
5	M	57	Ca esophagus	48	F	33	Melanoma
6	M	58	Ca pancreas	49	F	72	Melanoma
7	M	71	Ca esophagus	50	M	43	Ca salivary gland
8	F	73	Ca stomach	51	F	58	Ca tongue
9	F	60	Ca esophagus	52	F	75	Ca lip
10	M	80	Ca stomach	53	M	59	Ca salivary gland
11	M	56	Ca stomach	54	M	68	Ca tongue
12	M	58	Ca esophagus	55	F	64	Ca tongue
13	M	63	Ca stomach	56	F	57	Ca thyroid
14	F	63	Ca pancreas	57	F	28	Ca thyroid
15	M	63	Ca esophagus	58	M	63	Ca thyroid
16	M	88	Ca stomach	59	F	48	Ca salivary gland
17	M	59	Ca esophagus	60	F	67	Ca tongue
18	M	79	Ca esophagus	61	F	79	CML
19	F	81	Ca stomach	62	M	68	CML
20	M	80	Ca stomach	63	M	47	AML
21	F	68	Ca esophagus	64	M	41	HKL
22	F	76	Ca esophagus	65	M	79	CLL
23	M	60	Ca stomach	66	M	66	CLL
24	M	70	Ca bile duct	67	M	68	CLL
25	M	73	Ca colon	68	M	54	CLL
26	F	79	Ca colon	69	F	70	CLL
27	M	77	Ca rectum	70	M	37	HKL
28	F	75	Ca rectum	71	M	72	CLL
29	M	69	Ca colon	72	M	88	ALL
30	F	56	Ca rectum	73	F	51	NHL
31	F	73	Ca colon	74	F	80	NHL
32	M	79	Ca colon	75	F	28	NHL
33	M	77	Ca colon	76	M	60	HKL
34	F	60	Ca colon	77	M	47	SARC
35	M	57	Ca colon	78	M	21	SARC
36	M	77	Ca rectum	79	M	67	SARC
37	F	55	Ca colon	80	M	48	SARC
38	F	83	Ca colon	81	M	76	SARC
39	F	61	Ca colon	82	M	17	SARC
40	M	75	Ca colon	83	F	86	SARC
41	M	81	Ca colon	84	F	71	SARC
42	M	59	Ca colon	85	F	32	SARC
43	F	66	Ca colon				

Ca, cancer; Ca thyroid, papillary carcinoma of the thyroid gland; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; HKL, Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia, ALL, acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; SARC, sarcoma.

culated by assuming it occupied 5.9% of the patient's body weight.[11]

Experimental Protocol

All experiments involved the infusion of isotopes and the collection of blood samples. Multiple tracers were infused with each study, and each patient was studied once. Multiple tracers using the same isotopic label were not infused simultaneously; for example, ^{14}C-urea and ^{14}C-glucose. The rates of plasma glucose appearance and plasma glucose clearance were determined in all 85 patients using a primed constant infusion of 6$-^{3}$H glucose. The rate of net protein catabolism (NPC) was determined using a primed constant infusion of ^{14}C-urea in 33 patients, and the rates of plasma glucose oxidation and glucose recycling were not determined in these studies. The rates of plasma glucose oxidation and glucose cycling to lactate were determined in the remaining 52 patients. Because this required the infusion of both 6$-^{3}$H glucose and ^{14}C-labeled glucose, the rate of net protein catabolism in these patients was determined using a primed constant infusion of di-^{15}N urea.

At the start of each study, a primed constant infusion of isotopes was commenced through a forearm vein and maintained for a minimum of 3 hours. Blood samples were taken over a 60-minute period after 120 minutes of isotope infusion. The blood then was immediately centrifuged and the plasma was frozen.

Isotopes

Glucose kinetics were assessed using primed constant infusions of ^{14}C glucose and 6$-^{3}$H glucose.[1,12,13] The rate of net protein catabolism was obtained using primed constant infusions of ^{14}C-urea or di-^{15}N urea as we have described previously.[1,12,13] Plasma glucose and urea specific activity was determined as described elsewhere,[1,12,13] as was the plasma enrichment of di-^{15}N urea.[13,14]

Calorimetry

Indirect calorimetry was performed using an ADC CO2 Analyser (Hoddesdon, United Kingdom), and the rate of oxygen consumption in the postabsorptive state measured directly using a Sybron Taylor Oxygen Analyser (Hertsfordshire, United Kingdom).

Statistical Analysis

The degree of correlation between the estimated weight of tumor tissue present and the metabolic indices was determined using a regression analysis.[15]

Results

Protein Metabolism

A positive correlation ($r^2 = 0.80$) was found between the rate of plasma urea appearance and the rate of net protein catabolism and the bulk of tumor present (Fig. 1).

Glucose Metabolism

The bulk of tumor present was positively correlated both with the rate of plasma glucose appearance ($r^2 = 0.72$; Fig. 2) and the rate of plasma glucose clearance ($r^2 = 0.70$; Fig. 3). A negative correlation ($r^2 = 0.72$; Fig. 4) existed, however, between the percentage of glucose uptake oxidized by tissue and tumor bulk, and this was associated

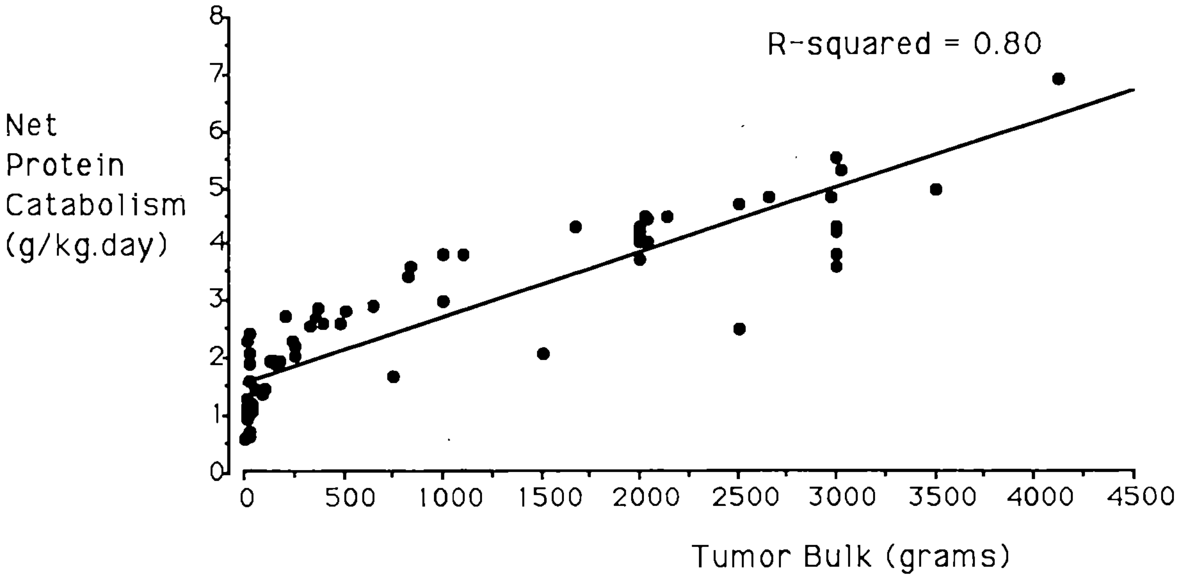

FIG. 1. Tumor bulk *versus* the rate of net protein catabolism in 85 patients with cancer.

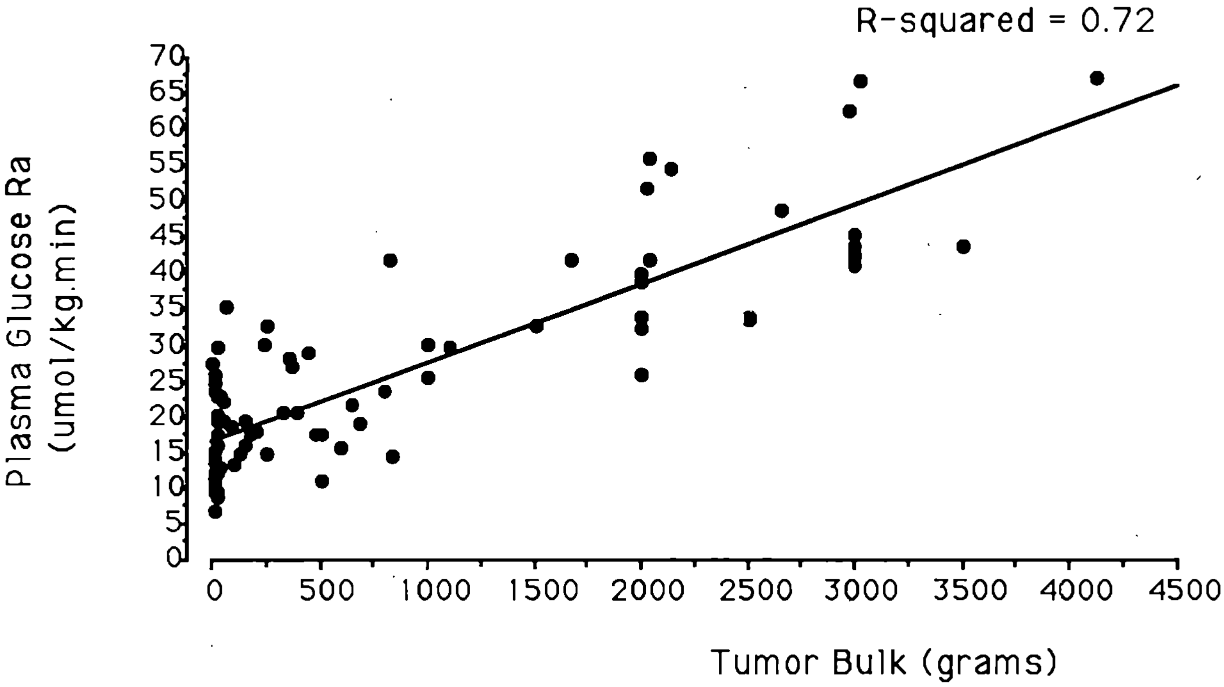

FIG. 2. Tumor bulk *versus* the rate of plasma glucose appearance. Ra, rate of appearance.

with a proportional increase in the percentage of tissue glucose uptake recycled to lactate (r^2 = 0.62; Fig. 5).

Oxygen Consumption

The volume of oxygen consumed per minute was positively correlated with tumor bulk (r^2 = 0.79; Fig. 6).

Discussion

This investigation has shown that the abnormalities in energy/substrate metabolism seen in the oncology patient are closely related to the quantity of malignant tissue present. Patients with a small tumor bulk are metabolically similar to normal volunteers,[1] and the alterations in intermediary metabolism characteristic of the oncology pa-

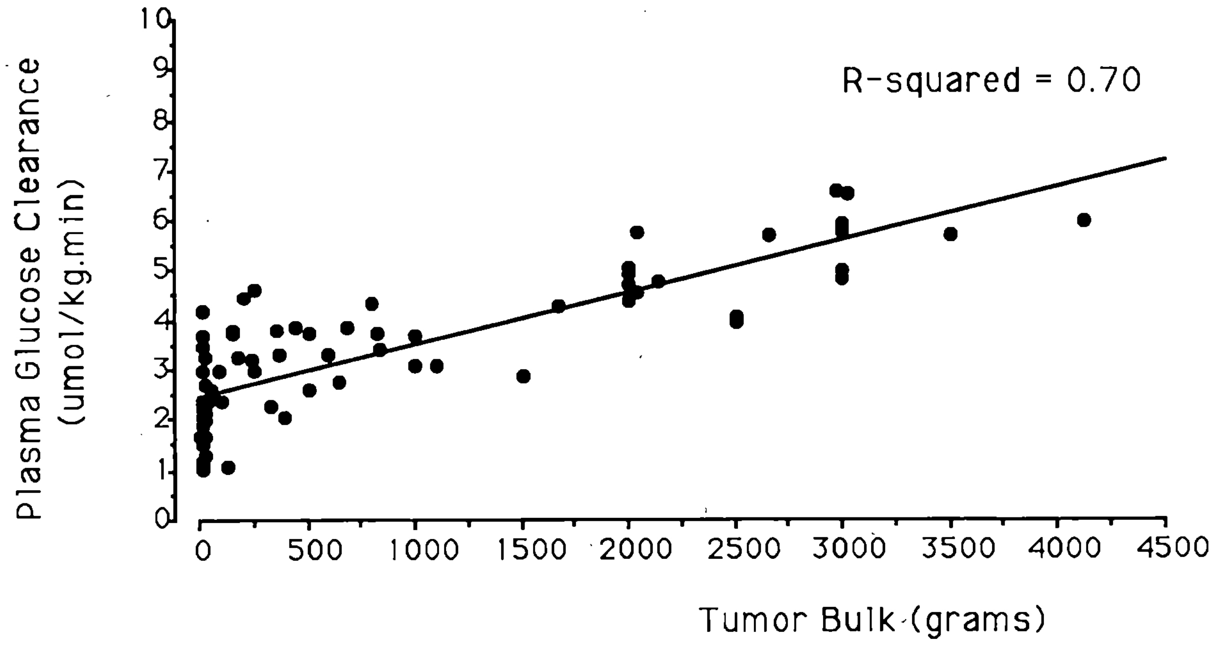

FIG. 3. Tumor bulk *versus* the rate of plasma glucose clearance.

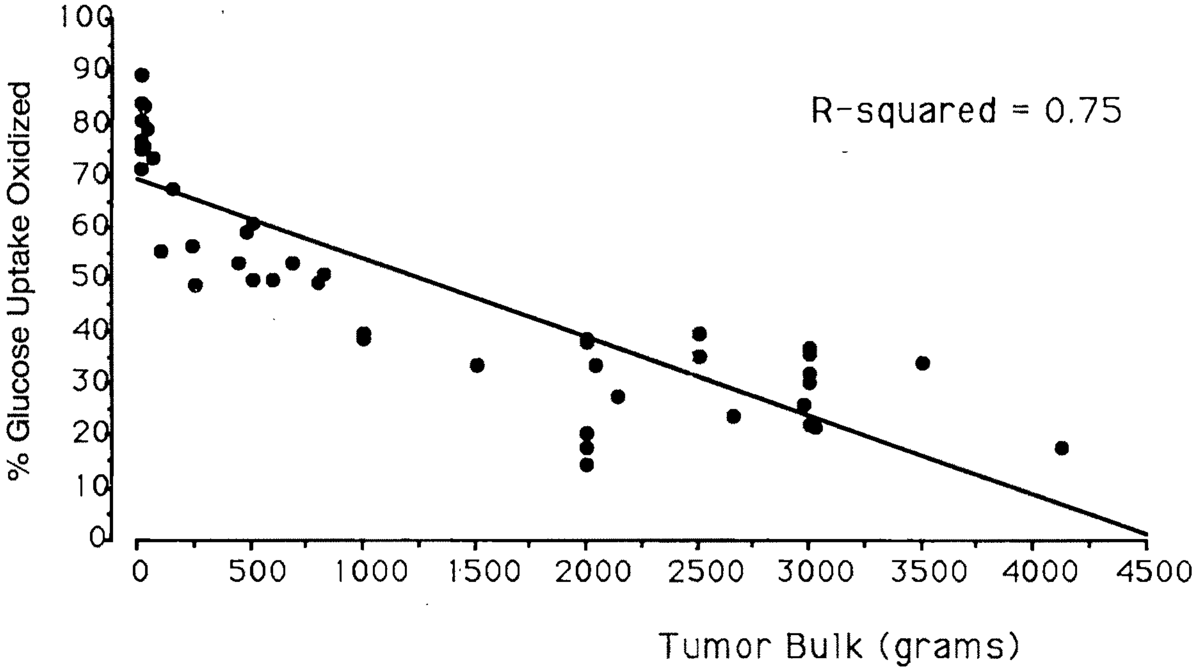

FIG. 4. Tumor bulk *versus* the percentage of tissue glucose uptake oxidized to carbon dioxide.

tient become increasingly marked as the tumor increases in size.

Although this investigation was not conducted in a prospective manner, we believe it is useful because a large standardized group of cancer patients have been studied; all of whom had histologically proven and accurately staged cancers with no concomitant sepsis or endocrine disease. In this way, we have been able to eliminate a number of potentially confounding variables. In addition, this methodology enabled independent measurements of tumor weight by histopathologists assessing the resected specimen and radiologists reviewing diagnostic CT and

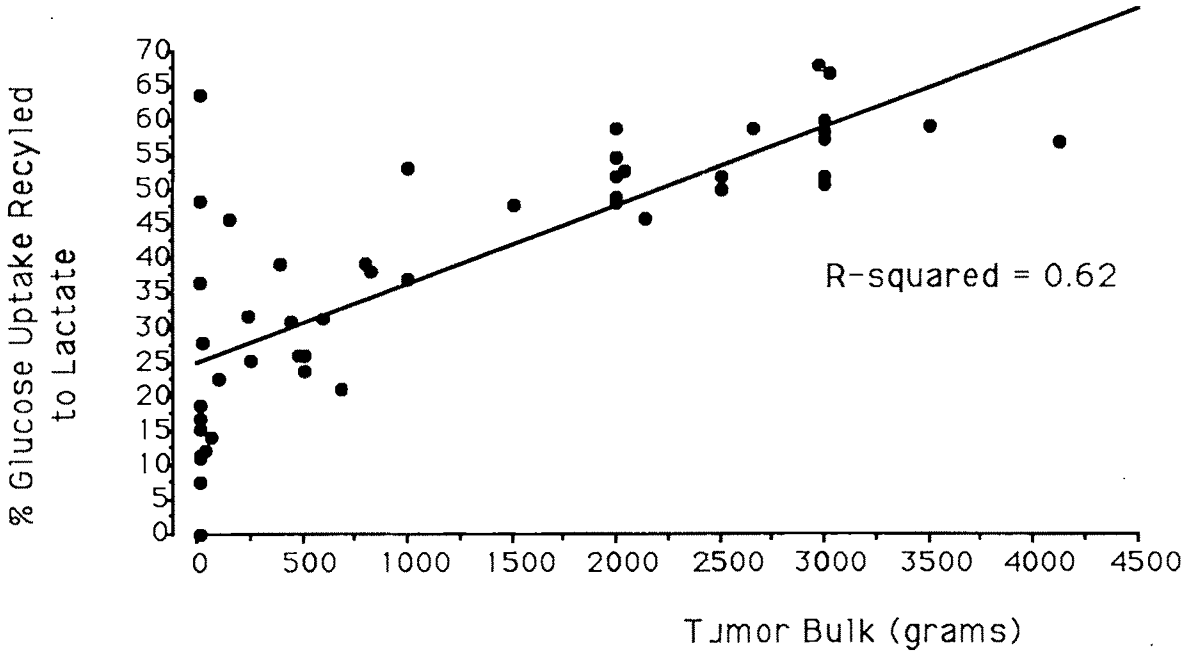

FIG. 5. Tumor bulk *versus* the percentage of tissue glucose uptake recycled to lactate.

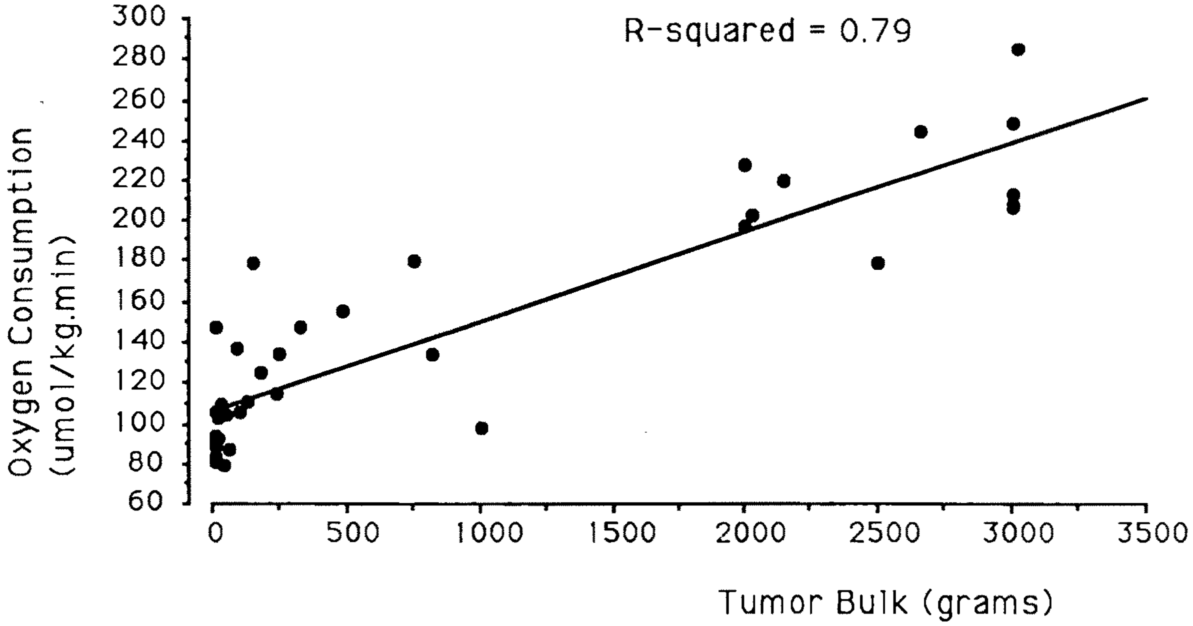

FIG. 6. Tumor bulk *versus* oxygen consumption in patients with cancer.

ultrasound scans. Measurement of tumor bulk using this methodology, however, may have underestimated the total volume of malignant tissue present in the patient with bulky metastatic disease. For this reason, although we have found a linear correlation between the measured metabolic parameters and tumor bulk, this relationship may become exponential in the large rapidly dividing tumor or in patients with large metastatic burdens. This is more consistent with the known kinetics of tumor growth.[16]

A progressive increase in oxygen consumption was seen with increases in tumor bulk. We have previously shown that patients with small colorectal cancers are normometabolic in comparison with normal volunteers,[1] whereas patients with disseminated cancers and bulky local disease often display increased energy expenditure up to 25% above normal.[7,17] Dempsey et al[18] have emphasized the considerable heterogeneity present in cancers of differing sizes by showing that patients with colorectal cancer may be normometabolic, hypometabolic, or hypermetabolic. Increased tumor bulk, however, tended to be associated with increased oxygen consumption. Because anaerobic glycolysis is characteristic of malignant tissue,[19,20] this increase in oxygen consumption may represent increased aerobic demand of nonmalignant host tissue, possibly for an acute phase response.[21]

One of the key findings of our study revolves around the marked alterations in glucose metabolism associated with increasing tumor bulk. Increasing tumor bulk is accompanied by a progressive decrease in the ability of the cancer patient to oxidize glucose completely to carbon dioxide, and there is a corresponding increase in the rate of glucose recycling to lactate. Other investigators have also documented similar findings in oncology patients.[1,2,12] Glucose recycling to lactate is an energy-expensive process resulting in a deficit of 2 moles of adenosine triphosphate for each mole of glucose recycled,[17] and this results in a net energy imbalance. Anaerobic glycolysis is a characteristic of malignant tissue,[19,20] and it is likely that glucose cycling to lactate occurs in tumor tissue. The manufactured lactate is then cycled back to glucose in the host liver.[22] The changes in the fate of available glucose therefore reflect increased use of available glucose by an increasing volume of tumor, leaving less glucose for oxidation by nonmalignant tissue.

The increased demand for glucose in the cancer patient is met by increased hepatic glucose production. This is associated with an increase in the clearance of glucose from plasma. Kokal et al.[2] have shown that patients with advanced colorectal cancers have a significantly higher rates of glucose turnover when compared with patients with localized colorectal cancers. Similarly, Holroyde et al.[22] found that patients with weight-losing metastatic cancer had increased rates of glucose turnover and glucose cycling to lactate. The association between progressively increasing rates of protein catabolism and elevated hepatic glucose production suggests that the negative nitrogen balance characteristic of cancer cachexia[9,10] results from an increased rate of gluconeogenesis from amino acids. We have previously shown that there is an increased rate of gluconeogenesis from amino acids in advanced upper gastrointestinal cancer,[1] and it is possible that the increased availability of substrate may "drive" hepatic glucose production. In addition, there is evidence that the key hepatic gluconeogenic enzymes are induced in cancer-bearing animals.[23]

The growth of malignant tissue results in progressive alterations in host energy/substrate metabolism that are directly proportional to the quantity of malignant tissue present. Carmichael et al[3] have suggested that growing tumor causes the translocation of host protein from skeletal muscle to areas of accelerated protein synthesis, the most prominent of which is the tumor itself. In addition, cancer bearing is also associated with abnormal energy metabolism, and it is clear that in the cancer patient, as opposed to the starving normal volunteer, there is an increased reliance on amino acids as a metabolic fuel, coupled with increasingly inefficient use of glucose. In contrast to other forms of metabolic stress, the response to cancer bearing is "aggressive and progressive" rather than an "all or nothing response" seen in patients suffering from trauma and sepsis.[24]

In summary, this investigation has shown the following:

1. Patients with small tumors usually have only minimal metabolic derangements.
2. The degree of metabolic abnormality is strongly correlated with the quantity of malignant tissue present.
3. Progressive tumor growth is accompanied by an increased rate of glucose cycling to lactate and a corresponding decrease in the percentage of available glucose completely oxidized to carbon dioxide.
4. The increased demand for glucose seen in patients with bulky tumors is met by an increase in hepatic gluconeogenesis, and this is probably partly fueled by amino acids mobilized from muscle.

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Endoscopic Transthoracic Sympathectomy in the Treatment of Hyperhidrosis

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A 5-year experience of 50 endoscopic transaxillary dorsal sympathectomies is presented. The procedure was successful in either curing or improving the symptoms of hyperhidrosis in the great majority of patients. The commonest side effects were compensatory sweating (75%) and gustatory sweating (48%); despite this, there was an extremely high level of patient satisfaction. Permanent Horner's syndrome did not occur. The procedure is effective, simple, cheap, and requires only an overnight stay; and is recommended as the method of choice for the surgical treatment of upper limb hyperhidrosis.

HYPERHIDROSIS MAY BE loosely defined as sweating above and beyond physiologic needs. Given the normal person-to-person variance of sweat production, it is difficult to be exact about a definition. Subjectively, hyperhidrosis occurs when sweating is clinically noticeable under conditions where it would not normally be expected, or is excessive in response to heat or emotional stimuli.[1] There is a paucity of epidemiologic data on hyperhidrosis; although it has been suggested that the incidence may be as high as 0.6% to 1% in certain populations.[2] Not only can it cause psychological and social problems, it also may result in occupational and educational difficulties.

It is important to distinguish secondary hyperhidrosis due to an underlying systemic illness from idiopathic or primary hyperhidrosis, usually occurring early in adolescence and characterized by excessive sweating in the hands (20%), axillae (37%), or both (43%), and often associated with plantar sweating.[3]

Hyperhidrosis has been reported as a symptom of central nervous system disorders with irritative lesions of the hypothalamus and hyperpituitarism. In addition, the sweats and fevers associated with many chronic disorders such as tuberculosis, lymphomas, and brucellosis are associated also with alterations of hypothalamic activity. Systemically, increased sweating has been noted as a symptom of such diseases as diabetes and hypoglycemia, thyrotoxicosis, pheochromocytoma, and carcinoid. It is therefore important to exclude any underlying condition when evaluating a patient with hyperhidrosis.

Nonsurgical treatment usually involves the use of topical astringents or absorbing powders, and these have proven very effective in the majority of mild cases. Medical management of more severe cases has included electrophoresis, which provides temporary relief; plastic wraps in association with aluminum salts[4]; and systemic anticholinergic drugs, which although providing relief from the sweating, have side effects such as loss of accommodation and dry mouth, which are poorly tolerated.[2]

Operative procedures for axillary hyperhydrosis include the excision of the eccrine glands at the apex of the axilla[5] and subcutaneous curettage[6]; however, if palmar hyperhydrosis is also to be treated, then sympathectomy is the only satisfactory and lasting surgical option.

The sympathetic innervation of the eccrine glands of the palm and axillae lie in the ganglia T2 through T4. It is these ganglia that must be ablated at operation. There are at least six open surgical approaches to these ganglia described, all of which carry a significant morbidity rate. These include the anterior supraclavicular,[7–9] the posterior paravertebral,[10] posterior midline,[11] anterior transthoracic,[12] axillary transthoracic,[13,14] and the axillary extrathoracic with first rib resection.[15] Minimally invasive approaches include percutaneous radiofrequency ablation,[16] and endoscopic axillary transthoracic.[17,18]

Although thoracic sympathectomy has long been known to inhibit palmar and axillary sweating, the operative risks of this "radical" procedure often have been thought to outweigh the potential benefits in this benign condition. We present the results of our own minimally

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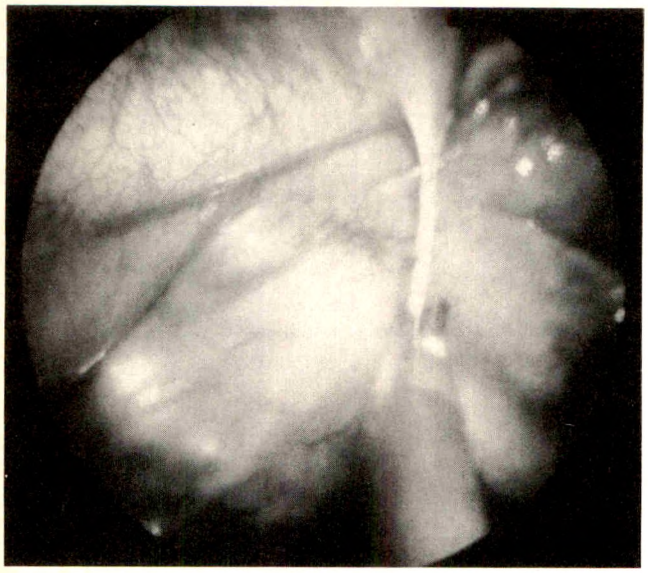

FIG. 1. Division of an apical adhesion in the left hemithorax.

invasive endoscopic technique and compare them with the morbidity of the open procedures.

Patients and Methods

Surgical Technique

A preoperative chest x-ray is taken to exclude any lung pathology, especially that which might predispose to adhesions. If encountered, simple adhesions can easily be divided endoscopically (Fig. 1).

The patient is anesthetized using a double-lumen endotracheal tube, and is placed on the operating table with both arms abducted to 90 degrees. A head-up position will facilitate the apex of the lung falling away on deflation.

A 0.5-cm incision is made in the anterior axillary line (to avoid the long thoracic nerve) over the third rib space. After clamping of the appropriate side of the endotracheal tube, a Verres's needle is inserted. The lung is slowly deflated over 2 to 3 minutes by instilling 2.0 L CO_2 into the interpleural space. In our experience, faster deflation has precipitated both ventilatory difficulties and hypotension (Fig. 2).

The Verres's needle then is removed and the laparoscope inserted. The upper sympathetic chain is then easily visualized lying over the necks of the ribs, from the second to the fifth or sixth ganglia (Fig. 3). A small second incision of a similar size is then made over the fourth space and the diathermy probe inserted. In obese patients, identification can be assisted by palpation using the probe. The second, third, and fourth ganglia, and their interconnecting fibers, then are diathermied (Fig. 4).

The lung then is reinflated under direct vision, and both incisions are closed with a single suture or Steristrips. A postoperative chest x-ray is performed in the recovery room to ensure no redevelopment of the pneumothorax. A unilateral procedure takes 20 to 30 minutes; a bilateral, approximately 45 minutes. The patients were discharged after overnight stay, although the procedure could be performed on a day admission basis. It has been our practice to perform the procedure on a unilateral basis, with contralateral sympathectomy undertaken 6 weeks later. With

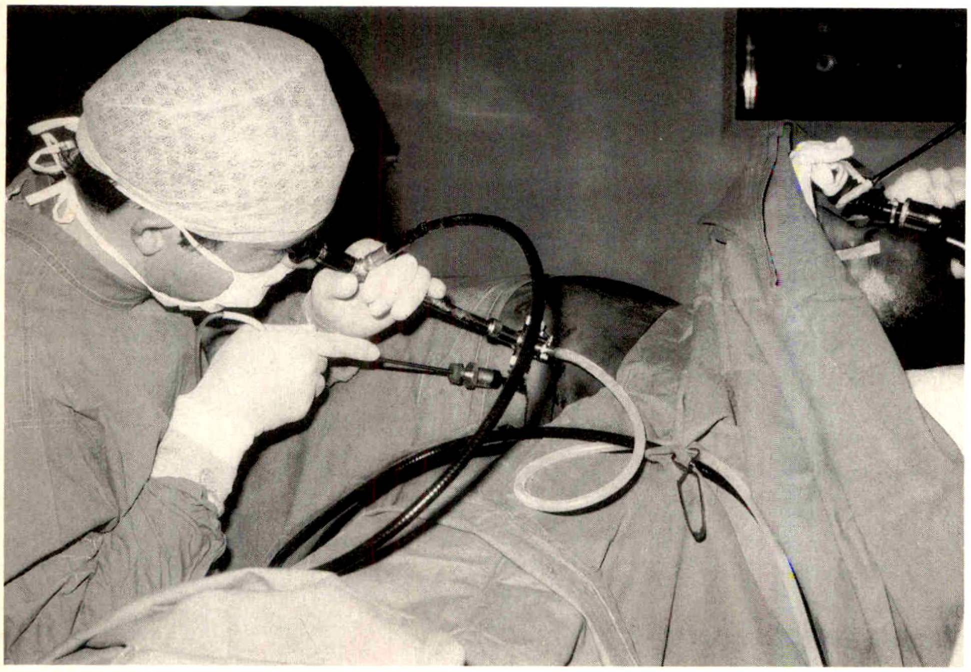

FIG. 2. Two-puncture technique with laparoscope in the anterior axillary line, third intercostal space, with the diathermy probe in the fourth space.

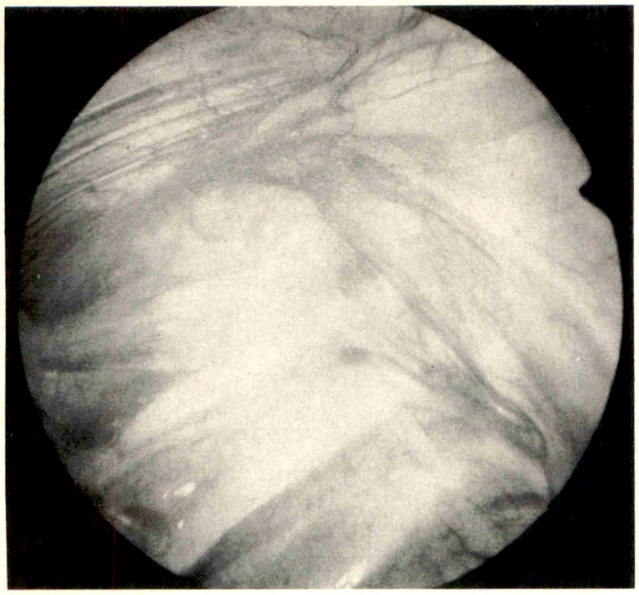

FIG. 3. Sympathetic chain and ganglia over the second to fifth ribs, right hemithorax. Note the collapsed azygous veins due to the head-up position.

increasing experience, however, bilateral sympathectomy has been undertaken without serious complications.

Patients then were contacted by a questionnaire or were interviewed. This included a linear analog scale to assess the completeness of the operation, and also the degree of trouble that any residual symptoms caused. Further questions were asked to ascertain whether certain complications had occurred. Patients were asked how long it took to return to work and sport, and also were given the opportunity to comment on any other features of the operation and its results.

Results

The results of 50 sympathectomies for hyperhidrosis were assessed. These showed a 2:1 female:male ratio. The average age of the group was 29.3 years (range, 16 to 59 years). The average length of follow-up was 26 months (range, 3 to 55 months). The distribution of symptoms showed that 52% of patients complained of sweating over their hands alone; 28%, axillae alone; and 24%, both areas.

Immediate complications at operation were minimal. No problems were encountered with bleeding. Only one of the patients required a chest drain for a subsequent pneumothorax. No patient complained of discomfort sufficient to delay discharge the following day. Two patients complained of chest infections after discharge home, which were treated by their general practitioners. There were no significant wound infections postoperatively and no subsequent problems with scarring.

Using linear analog scales, patients were asked to score both the right and left sides on a scale of 0 to 100 from "as bad as before" to "absolutely dry." They were also asked how troubled they were by their residual symptoms (Table 1).

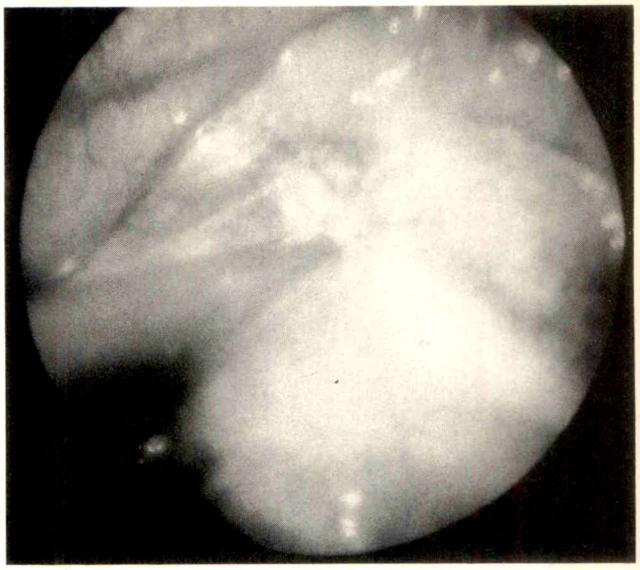

FIG. 4. Diathermy of the ganglion over the neck of the second rib, left hemithorax.

It is worth noting that the patient who scored a 40% "response" and a 30% "relief" scored her contralateral side 100% for both. This would suggest a technical failure, probably as a result of incomplete ablation. A second patient claimed absolutely no response at all in either axilla, which may represent poor patient selection.

Patients then were asked if they had noticed any increased sweating over other parts of their bodies. Seventy-five per cent replied that there was an increase in sweating over their trunks, some complaining also of sweating over their thighs and feet. This sweating was usually associated with hot weather or exercise. Even those patients who described the sweating as excessive volunteered comments that it was far preferable to their original complaint.

Patients were further asked whether they had experienced any new symptoms of sweating over their faces associated with eating. Forty-eight per cent said this was a new symptom, with a further 4% saying they had the feeling of sweating without actually perspiring. Many volunteered that spicy foods and cheeses were usually to blame.

TABLE 1. *Response and Relief Derived From the Linear Analog Scales in the Questionnaire*

Area Affected	% Response (Range)	% Relief (Range)
Hands only	95.3 (72–100)	98.1 (95–100)
Axillae only	71.3 (0–100)	77.0 (0–100)
Both areas	84.5 (60–100)	90.2 (70–100)

One patient developed a temporary Horner's syndrome after operation, which resolved spontaneously. In addition, one patient did complain of a severe postoperative neuralgia unilaterally, whereas another complained of slight paresthesia at the top of the arm and over the scapula.

Seventy per cent of patients returned to work within a week, and began playing their usual sports within 2 weeks.

Ninety-two per cent of patients were extremely satisfied with the results of their operation. The patient who suffered the postoperative neuralgia was cured of her hyperhidrosis. One patient's axillary hyperhidrosis failed to improve after the operation.

Discussion

The use of dorsal sympathectomy in the treatment of hyperhidrosis produces consistently good results. Our results compare favorably with those of open operations, giving between 89% and 100% resolution of sweating.[2,3,9,10]

With the exception of technical failures, virtually all patients gain relief of their palmar sweating. Axillary sweating, however, seems less well controlled; residual sweating, although not usually troublesome, occurs in approximately 20% of cases where sympathectomy is performed from T2 to T4 inclusive.[3] This theoretically may be improved by ablation of the T5 ganglion.[19] In doing so, however, the extent of compensatory sweating may well be increased. The importance of ablating T4 in the control of axillary sweating is supported by the fact that using the supraclavicular approach, which finds T4 relatively inaccessible, thereby confining ablation usually to T2 and T3,[18] yielding results of only 8% complete axillary drying, and 78% partial drying.[2]

Axillary skin excision also may be used in conjunction with sympathectomy[2]; however, as a lone procedure it produces a 19% failure rate, with only "fair" results in a further 10% of patients.[9] T4 is easily accessible endoscopically, and to excise axillary skin would negate the advantage of minimal scarring and short hospital stay while only conferring a small additional benefit.

The following problems were common to all sympathectomies, whatever the technique.

Compensatory Sweating

This occurred characteristically over the trunk and upper thighs. It probably represents a thermoregulatory response and is a common occurrence, ranging from 37%, up to 75% in our own series.[3,5] Thirty per cent of the patients described the sweating as excessive, especially on exercise and in hot weather, yet nearly all preferred this to their original complaint; several also mentioned that the sweating showed a tendency to improve with time. This may mirror some return of sweating to the palms and axillae,[2,8,10] which we also observed in 16% of cases. This was only minor and never approached the original hyperhydrotic state.

Gustatory Sweating

We found this to be far commoner than in previous reports. Only 2% of Kux's patients complained of this being a problem[3]; however, on direct questioning some 48% of our patients noticed this. A further two patients said they experienced the sensation of sweating when they ate, without actually sweating. Interestingly, many volunteered that cheeses and spicy foods were usually to blame. Frey's syndrome, a similar problem after parotidectomy, is thought to be due to inappropriate regeneration of nerve fibers[19]; however, that seems unlikely in this case, where sweating occurs over any part of the face or neck. In addition, the "phantom sweating" experienced by some of our patients strongly suggests a central component.

Postoperative Horner's syndrome is largely a complication of the supraclavicular approach. Mild, transient Horner's is reported as often as 43%,[2] with permanent symptoms occurring in from 2% to 8%.[2,9,18] This is not a problem with either the open or endoscopic transaxillary techniques or the dorsal approach.[3,10] In fact, the stellate ganglion is well protected by the dome of the pleura, and only the distal third is visible to the endoscope. It has been suggested that the high incidence of Horner's syndrome in the open operations is due to anatomic variance. This is unlikely, because none of the transaxillary approaches carry an equivalent risk, and other studies have shown a decrease in the incidence of Horner's with operative experience. There was also one recorded case of phrenic nerve damage using the supraclavicular approach.[18] Neuralgia is a rare occurrence but has been reported in other series. The exact mechanism of this is unknown.

Chest drainage for pneumothorax occurred with a frequency of 4% to 6% for the supraclavicular operations,[2,8,18] with 93% of patients requiring drainage after the open transaxillary approach.[14] In our endoscopic series, we had to insert one chest drain (2%), other endoscopic series showing similar figures.[3]

Wound infection rates endoscopically were negligible in both our series and that of Kux; however, open surgery showed a rate as high as 14%.[14] Operative time varied, but the average for a bilateral open operation was 90 minutes. This time was halved endoscopically. Hospital stay averaged 3 days[10] to 7 days[14] for open operation; endoscopically, this was an overnight procedure, with 70% of patients back to work within 1 week.

Our technique differs from that described by Kux[3] in several ways. The entire procedure is performed under general anesthetic, with the patient in one position from the start of the operation. The use of CO_2 to produce the pneumothorax has the advantage that any residual gas left behind after the operation is rapidly absorbed. Using the double-puncture technique, a smaller laparoscope may be used, allowing greater mobility of movement within the tight intercostal space, and theoretically decreasing the chance of damage to the intercostal vessels and nerves. Advances in optics, however, may soon allow the development of smaller laparoscopes equipped with operating channels.

In summary, the results of endoscopic sympathectomy compare favorably with those from all other open techniques. It has the added advantage of simple access to T4, which is important in the control of axillary sweating. The risk of neural damage, including Horner's syndrome, is virtually absent. The short hospital stay and early return to work are significant financial benefits. It offers minimal postoperative discomfort and excellent cosmetic results in patients who fail medical management. The technique is easily learnt, and requires no additional capital outlay in a hospital already performing routine laparoscopy. Patients should be warned of the potential side effects of compensatory and gustatory sweating, but they may be reassured that the vast majority of patients find these symptoms only a minor inconvenience in comparison with their original complaint. In view of its consequences, they also should be warned of the rare possibility of neuralgia. Because hyperhydrosis is essentially a benign condition, any operation must keep morbidity to a minimum. The endoscopic transaxillary approach seems to fulfill this criteria, while giving as good results as any of the open operations for palmar hyperhydrosis and better single-stage results if axillary sweating is to be controlled as well. Our results complement those of Byrne et al.,[20] confirming the endoscopic transthoracic sympathectomy as the treatment of choice in the surgical treatment of hyperhidrosis.

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BOOK REVIEWS

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Principles & Practice of Surgery, 2nd Edition. A. P. M. Forrest, D. C. Carter, and I. B. Macleod. 729 pp. Naperville, Illinois: Churchill Livingstone, 1991. $42.00.

THIS IS THE SECOND EDITION of this successful book, providing a text for undergraduates and early postgraduates studying surgery. The first edition (1985) was modeled on the established *Davidson's Principles and Practice of Medicine.* As an economical paperback, an aim is to "update the work" and "keep pace with the rapidly changing developments in surgery." It achieves some of this by use of simple line drawings (Anne McNeill). These are of high quality and are informative and supplement the text, which is well edited in a uniform style. There are no photographs or radiographs, which would add to the value of the text. One or two illustrations give unclear messages or depictions; for example, those showing onychogryposis and a melanoma. The skin graft coming through the mesher looks as though it is being converted into a seaweed rhizome!

There are one or two mistakes that should not have crept through: it is "thallium," not "gallium," for parathyroid imaging, and laparoscopic cholecystectomy, not cystectomy—yet! I think it unfair to call the spleen friable—it is only friable in a surgeon's hand or if it has been in an altercation with a motor car! Differences of opinion might be: that malignant ascites can be shunted as well as that due to other causes and that a bilateral posterior approach for bilateral adrenalectomy is easier and associated with less morbidity than an anterior approach.

The last sections of the book deal with urology, neurosurgery, practical procedures, and an apposite chapter on medicolegal matters. There are chapters that cover cardiothoracic surgery and transplantation.

I wonder if the dynamics of writing, typesetting, and publication would have allowed more mention of the surgically related problems to human immune deficiency virus (HIV) infection and the revolution in laparoscopic techniques. Both these areas are rapidly changing developments in surgery and should feature in future editions in much greater depth. Already in some institutions students may not see an open cholecystectomy, and surgical trainees may well carry out the laparoscopic procedure never having performed open cholecystectomy.

One only needs to have operated in the same theater as Joseph Lister to appreciate the surgical presence in the Royal Infirmary, Edinburgh. That presence is conveyed in this book by the three senior editors, who hold consultant posts in this institution. There are 12 other contributors, a few of whom work south of the Scottish border, and there are even contributors from Glasgow! The work is authoritative and easily read. It will be established and equivalent in stature to the much longer-standing *Principles and Practice of Medicine.* As with most things from north of the border, this is an amiable and effective Scottish Companion.

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Comprehensive Textbook of Oncology, 2nd Edition. Volumes 1 and 2. A. R. Moossa, Stephen C. Schimpff, and Martin C. Robson. 1918 pp. Baltimore: Williams & Wilkins, 1991. $175.00.

IN THE PREFACE to the first edition, the editors state that their objectives were to present an overview of oncology that would be a starting point for a comprehensive understanding of cancer. In the second edition of this multi-authored, two-volume text, the editors have succeeded admirably in providing a masterwork of oncology, fulfilling their stated goals.

The scope and complexity of the topics in this 1918-page text is exemplified by its 269 contributors. Nonetheless, the editors have been able to unify the book by its highly organized format. The book begins with new discussions about the basic concepts of cancer biology with comprehensive reviews of normal cell biology and control of growth to the molecular biology of tumor development, with special emphasis on viral carcinogenesis, oncogenes, and the immunology of cancer. The next section is devoted to concepts of cancer evaluation, with specific chapters on screening and prevention, patient evaluation, and staging, with a specific section on tumor markers. There are specific chapters on techniques of pathologic evaluation and diagnostic imaging. This is followed by a long section on concepts of cancer therapy, including chapters on the principles of surgical therapy with detailed discussion about the use of lasers and cryosurgery. There are chapters on radiation therapy, chemotherapy, and other therapeutic approaches, including hypothermia, photodynamic therapy, and alternative and unorthodox methods of cancer therapy.

After this broad overview of the principles of oncology with emphasis on basic biology and fundamental principles, the book then approaches specific neoplasms by organ system. These sections are well written and address specific management of cancers in each of the organs, along with a section on the acquired immune deficiency and a section on childhood cancer.

Finally, the authors discuss the complications of neoplasia and its treatments, along with ethical and socioeconomic issues. Also included are useful discussions of cancer staging, chemotherapeutic and therapeutic regimens, and oncologic emergencies. These are appended to allow for easy access.

Overall, this comprehensive textbook provides a firm foundation for the evaluation of patients with malignancy and is an essential requirement for all those with an interest in oncology and those caring for patients with cancer. Not only is the specific biologic basis for rational evaluation and management discussed, but the contributors have included updated bibliographies and very good illustrations when appropriate. The text is handsomely bound, and the size of the volumes allows for ease of use.

In summary, the editors have clearly demonstrated their ability to provide a comprehensive textbook of an ever-enlarging topic. They are to be congratulated for updating us in such a timely and concise manner. This book will predictably find wide use among oncologists and surgeons.

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A Color Atlas of Endovascular Surgery: Interventional Techniques in Vascular Disease. Rodney A. White and Geoffrey A. White. 200 pp. Philadelphia: JB Lippincott, 1990. $129.50.

DRAWING ON THEIR unmatched experience in endovascular surgery, the authors have compiled a delightful book to illustrate the many facets of this burgeoning field. After an initial discussion of the theories of atherogenesis, there are chapters on intraluminal access techniques, balloon angioplasty, lasers, atherectomy, and angioscopy. Shorter chapters deal with intravascular stents, other endovascular techniques (such as thrombolytic therapy), intravascular ultrasound, and laser tissue fusion.

Visually, this very pretty book is filled—as the title implies—with colorful pictures. The technical quality of the illustrations is excellent. Line drawings, arteriograms, and photographs of techniques, instruments, gross specimens, histologic slides, and angioscopic images are all clearly reproduced and attractively displayed. Each of the 319 figures is accompanied by a well-written explanatory legend, located adjacent to the figure. As befits an atlas, the text is sparse, occupying only 20% to 30% of the average page. The entire volume can be read easily in one sitting.

One ordinarily expects a surgical atlas to describe in some detail the steps necessary to perform an operative procedure. The reader of this book, however, will come away with only a vague notion of how to perform arterial catheterization, angioscopy, balloon angioplasty, atherectomy, or laser therapy. Although some theory and background data are provided, this material is of a superficial nature. Yet, the level of discussion presupposes a modicum of knowledge and a passing familiarity with technical jargon. For example, nowhere in the text are the terms YAG or excimer defined. The neophyte needs more substantive information and much more detail than the book supplies, and the experienced endovascular surgeon will search in vain for "gems" that will help perfect his or her technique. In essence, the content resembles that of a well-illustrated "slide show," familiar to those who attend continuing medical education lectures.

This is the type of book that should grace a surgeon's coffee table. It is fun to read, serves an introductory purpose, and the beautiful pictures can be used to illustrate endovascular surgical concepts, procedures, and instruments to patients, students, or residents. Few, I expect, will turn to it frequently as a source of information.

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The Spinal Cord Injured Patient: Comprehensive Management Bok Y. Lee, Lee E. Ostrander, George Van B. Cochran, and William W. Shaw. 360 pp. Philadelphia: WB Saunders, 1991. $70.00.

THIS MULTI-AUTHORED and multi-edited book on spinal cord injury consists of 29 various chapters dealing with this important subject. Each chapter is well written, making the reading easy. The topics are quite varied. Certain subjects seem to receive more emphasis than is warranted, as evidenced by some of the chapter headings: for example, Chapter 20—The Role of Mattresses and Beds in Preventing Pressure Sores; Chapter 23—Paralysis Secondary to Abdominal Aortic Aneurysm, Chapter 11—Renal Insufficiency in Patients with Spinal Cord Injury. Each of these topics are important, but should be subcategories of larger chapters.

Spinal cord rehabilitation is covered in less than 40 of the 336 pages. Chapter 2 on Deep Vein Thrombosis (DVT) seems a little thin. Pneumatic compression is addressed, but after the acute phase is over and the patient is begun on rehabilitation, DVT prophylaxis usually does not use this form of therapy. Also, the diagnostic efficacy of various tests available in suspected DVT would be helpful.

Chapter 4 misses the new high-dose steroid data, which is probably a simple matter of publication deadlines. Chapter 10—Urology is a comprehensive treatment of the subject, as is Chapter 17 on pressure sores. Although short, Chapter 24 on rehabilitation introduces most of the issues that arise in rehabilitation of individuals with spinal cord injury.

There are extensive chapters on dealing with the surgical management of the acute spinal cord injury patient, and these are dealt with thoroughly and seem up-to-date. This book also provides a reasonable amount of information and alternatives to treating difficult problems of the spinal-cord–injured patient, for example, heterotopic ossification and autonomic dysreflexia.

The rather new role of sports activities for the spinal cord injured is not covered. Also, attitude development of our society toward individuals with a "handicap" is only mentioned, but is a major issue with those who have a spinal cord injury.

The photographs and geographic studies, including magnetic resonance imaging (MRI) scans, are an excellent addition to an up-to-date textbook.

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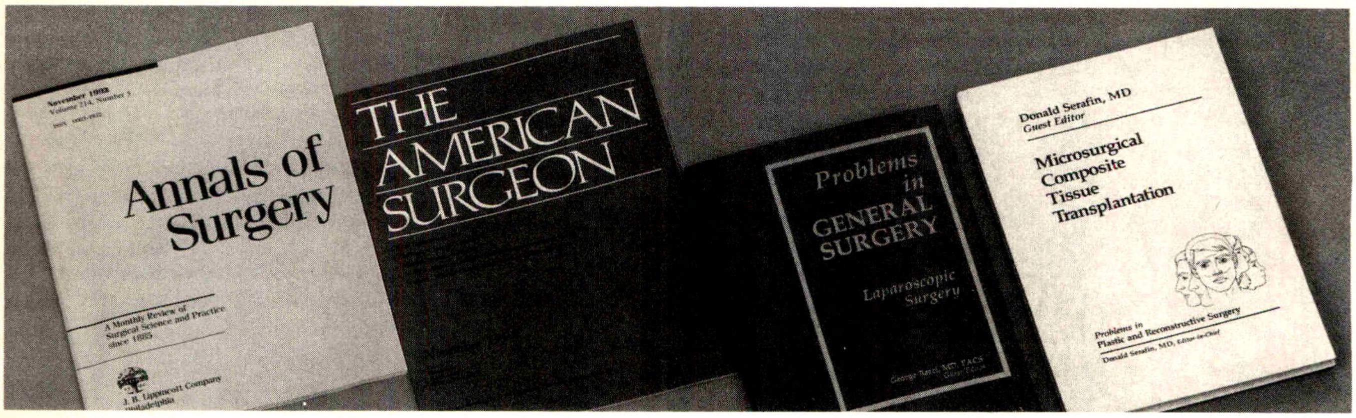
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Controversies and Advances in Primary Hyperparathyroidism

Primary hyperparathyroidism is a very common disease in the United States. It is increasingly being recognized because of the widespread availability of multiphasic screening for hypercalcemia and double-antibody immunoassays for intact parathyroid hormone. Approximately 100,000 new cases are diagnosed each year, and women are affected twice as often as men. Surgery is the major potentially curative form of treatment. Because of the common occurrence of this debilitating and life-threatening disease, general surgeons play an important role in the management of patients with primary hyperparathyroidism.

In this issue of the *Annals of Surgery,* Kaplan and Yashiro update the reader on important issues in the management of patients with primary hyperparathyroidism. Their review stresses the necessity of surgical "experience" for the successful management of these patients.[1] Experience is essential for diagnosis, identification of parathyroid glands, and determination of the true extent and nature of the disease (hyperplasia *versus* adenoma *versus* carcinoma). The review provides numerous helpful hints and suggestions for improved management of these patients. From the standpoint of how to do it, it provides valuable information and is well worth careful consideration. There are additional current controversies and research in this fast-moving field that also should be considered, however. This editorial will attempt to highlight a few of the more important recent developments that will likely affect the management of patients with primary hyperparathyroidism.

Because of the use of multiphasic screening, many patients with the biochemical diagnosis of primary hyperparathyroidism are asymptomatic. These patients have minimally elevated serum levels of calcium and parathyroid hormone, but do not have symptoms or signs of bone, renal, gastrointestinal, or neuromuscular disease. A question arises about the proper management of these patients. Who can be safely followed without surgery and should they be? These questions were recently addressed by a consensus development conference at the National Institutes of Health.[2] The group stated that there is a population of patients with primary hyperparathyroidism that can be safely managed medically and should be carefully followed. Patients with only mildly elevated serum levels of calcium, no prior episodes of severe hypercalcemia, and normal renal and bone status are eligible for nonsurgical management.[2] This is a controversial point and one that deserves more debate. First, the ability of meticulous surgery to cure patients has been unequivocally demonstrated over and over again, and the success rate is probably greater than 95%.[2] Second, the typical patient with no family history of endocrine or parathyroid disease who is diagnosed by screening most likely will have a parathyroid adenoma as a cause of the primary hyperparathyroidism and will be more readily cured by surgery than the more complex patients with familial hyperparathyroidism and hyperplasia. Third, as a parathyroid surgeon I have been impressed that patients with asymptomatic primary hyperparathyroidism are not really asymptomatic. For example, patients have subtle symptoms like memory loss, personality change, inability to concentrate, exercise fatigue, back pain, and others that are not uncommon in daily living, which may completely disappear with successful surgery. Finally, the surgery can be performed safely with very minimal complications (<1% recurrent laryngeal nerve injury rate), no transfusion requirement, and essentially no operative deaths. It is unclear whether careful follow-up with repetitive measurements of bone densitometry and chemistry determinations will be preferable over a simple surgical procedure that has a high likelihood of success, minimal complication rate, and the possibility of relieving subtle, but potentially significant, symptoms.

Another controversial point is the use of radiographic imaging studies to localize the abnormal parathyroid gland or glands in patients who are undergoing initial operations for primary hyperparathyroidism. Most experts agree that the use of imaging studies is not indicated and can be costly and misleading.[1,2] However, many physicians commonly obtain these studies and use them to confirm the diagnosis of primary hyperparathyroidism and to determine whether or not to perform surgery. Imaging studies cannot reliably accomplish either task. Noninvasive studies have a 15% false-positive rate and only a 60% true-positive rate, which are clearly inferior to surgery that has a 95% success rate.[2] The diagnosis is made solely by the determination of abnormal serum levels of calcium and parathyroid hormone, and the decision to operate is based either on symptoms or unequivocal evidence of the disease. Radiographic imaging studies do not have a role in either.

Exciting new findings are providing insight into the cause and molecular pathology of primary hyperparathyroidism. In patients with multiple endocrine neoplasia type 1 (MEN-1), hyperparathyroidism is caused by hyperplasia of all four glands, and even patients whose remaining glands appear to be normal have a tendency toward recurrent enlargement, because there is a 50% recurrence rate with long-term follow-up.[3] A parathyroid mitogenic factor had been described in the plasma of patients with MEN-1. This substance stimulates the proliferation of bovine parathyroid cells and resembles basic fibroblast growth factor.[4] However, polyclonal hyperplasia secondary to a growth factor is not the only cause of enlargement of parathyroid glands in MEN-1 patients, because monoclonal enlargement has also been described.[5] Allelic loss (loss of heterozygosity) from chromosome 11 was found in most abnormal parathyroid glands from patients with primary hyperparathyroidism in the setting of MEN-1. Ten of sixteen abnormal parathyroid glands from 14 different patients had losses of alleles from chromosome 11. Glands with losses were larger than those without, suggesting that a monoclonal growth may develop after a phase of polyclonal hyperplasia.[5] Because the gene associated with MEN-1 is also located on chromosome 11 (11 q 13),[6,7] it may normally inhibit tumor proliferation, and tumors could originate from inactivation of one or both alleles.

Similar genetic anomalies also have been described recently in sporadic parathyroid adenomas: a novel gene rearrangement involving the parathyroid hormone gene on chromosome 11[8,9] and allelic loss from at least two regions of chromosome 11.[5,10] Allelic loss from chromosome 11 was found in a significant proportion of sporadic parathyroid adenomas. This frequency of allelic loss has several implications. First, it is consistent with the theory of a monoclonal origin for parathyroid tumors. Second, it is also consistent with the hypothesis that inactivation of a tumor suppressor gene contributes to the initiation or evolution of benign parathyroid tumors. Analogous loss of the normal homologue of a growth suppressor gene has been observed in acoustic neuroma, colon carcinoma, Wilms', and other tumors. Presumably the action of these genes is recessive at the cellular level. Another, less common (3%) mechanism of parathyroid adenoma initiation is DNA rearrangement involving the parathyroid hormone (PTH) gene. One of these DNA rearrangements has been shown to juxtapose the first intron of the PTH gene on the short arm of chromosome 11 to band q13 on the long arm and form an oncogene (PRAD-1).[11,12] PRAD-1 has been cloned and encodes for a protein of 295 amino acids with sequence similarities to cyclins,[12] which act as stage-specific regulators of progress across the cell cycle. PRAD-1 has been implicated in cancers, including breast and squamous cell carcinoma, but oncogenes have not previously been implicated in growth of benign tumors. Thus, the initiation of parathyroid tumor growth is heterogeneous, from deletion of a suppressor gene in a significant proportion of tumors, to induction of an oncogene in a minority of tumors.[7-12]

Beside these most impressive advances in the molecular pathophysiology and initiation of parathyroid neoplasia, advances in the clinical and operative management of patients with parathyroid neoplasms also deserve attention and consideration. As mentioned, the diagnosis of primary hyperparathyroidism is dependent primarily on abnormally elevated circulating levels of PTH, and the current pathologic analysis of parathyroid glands (normal *versus* adenoma *versus* hyperplasia *versus* carcinoma) is, at best, an inexact science. Therefore, an intraoperative functional assay for the determination of surgical correction of hyperparathyroidism is valuable. These assays are especially helpful during tedious reoperations on patients with parathyroid hyperplasia who have a higher incidence of recurrent disease and who have had abnormal glands removed at multiple institutions by different surgeons. Intraoperative determination of urinary cyclic adenosine monophosphate levels[13] or serum PTH levels[14] have been shown to correlate with successful resection of all abnormal parathyroid tissue. These measurements provide the surgeon with functional confirmation of the outcome during the procedure.

Another technical advance is the use of high-resolution near-field real-time ultrasound during reoperations for primary hyperparathyroidism.[15] Intraoperative ultrasound (IOUS) is able to image abnormal parathyroid tissue and direct the surgeon to the parathyroid tumor. It is especially adept at detecting tumors that are within or near the thyroid. It is valuable because it can take the place of extensive tedious dissection in scarred reoperative fields. We have found that approximately 20% of parathyroid adenomas removed during reoperation are within the thyroid and that IOUS will localize these tumors and allow resection without removing the entire thyroid lobe. Finally, another technical advance is the nonoperative management of mediastinal parathyroid adenomas by angiographic ablation. Angiographic ablation is the purposeful injection of extra contrast material into the feeding vessel of a parathyroid tumor selectively to destroy it. At the National Institutes of Health, where there is a large experience with parathyroid reoperations and localization, radiologists have treated 27 patients with mediastinal parathyroid adenomas by this method.[16] Long-term control of primary hyperparathyroidism was achieved in 17 (63%) with no complications and minimal pain. The remainder could have the gland removed easily by median sternotomy. These results suggest that angioablation may be the initial procedure of choice for patients with mediastinal parathyroid adenomas identified by angiography and that operation can be reserved for those who fail ablation.

The management of patients with primary hyperparathyroidism has rapidly evolved since the first patient was treated surgically in 1925. The future appears to be with the use of sensitive molecular biology techniques to determine the origin of the disease and to develop new diagnostic as well as localization techniques. As stated by Kaplan and Yashiro, an important criterion for successful surgical outcome is the experience of the operating surgeon.[1] The challenge for teaching hospitals and professors of surgery is transferring that experience to surgical residents. Based on the high incidence of the disease, the fact that in most patients it is a progressive disease, and the potential curative outcome of surgery, the number of parathyroid explorations should continue to increase in the future. Young surgeons will not only need to know the principles of parathyroid surgery and technical options for more difficult cases, but they will need to understand the mechanisms of parathyroid tumorigenesis to continue to ensure excellence in the management of these patients.

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WHAT'S NEW IN GENERAL SURGERY

Primary Hyperparathyroidism in the 1990s

Choice of Surgical Procedures for This Disease

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Many advances have occurred in recent years in the diagnosis, localization, and treatment of primary hyperparathyroidism. Several different operative choices for primary hyperparathyroidism also have been proposed—a unilateral approach *versus* the standard bilateral parathyroid exploration. The unilateral approach is based on the concept that if an enlarged parathyroid gland and a normal gland are found on the first side of the neck that is explored, then this is an adenoma and the second side should not be explored. Only if both glands on the initial side are recognized to be abnormal is the second side explored. The theoretical advantages of this unilateral approach are a decrease in operative morbidity rates—hypoparathyroidism and nerve injuries—and a decrease in operative time. Furthermore, proponents argue that if persistent hyperparathyroidism occurs, the second side can be easily explored because it was previously untouched. In the hands of several expert parathyroid surgeons, excellent results have been achieved. However, the unilateral approach has a number of disadvantages. It places considerable pressure on the surgeon and pathologist, for they have only one parathyroid gland other than the large one to examine. There is a significant potential risk of missing double adenomas or asymmetric hyperplasia because the second, ipsilateral parathyroid gland may appear normal or near normal in these conditions. This could lead to an increased incidence of persistent or recurrent hyperparathyroidism. Furthermore, a significant reduction of operative time may be questioned, especially when the time for performing special fat stains, which often are performed with unilateral explorations, is added. Finally, even if the intent is to perform a unilateral exploration, a bilateral exploration will be necessary about half of the time. The authors strongly recommend a bilateral parathyroid exploration for all patients undergoing an initial parathyroid operation. In cases of adenoma, bilateral visualization of normal parathyroid glands and careful biopsy of only one of them will minimize hypoparathyroidism. This operative approach will lead to better results, especially for the less experienced parathyroid surgeon.

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SURGERY FOR PRIMARY hyperparathyroidism (HPT) is usually one of the most gratifying of all operations; however, at times, it can be one of the most frustrating. Parathyroidectomy has been practiced for about 65 years.[1] During that time, a great deal of knowledge of the anatomy, embryology, pathology, and physiology of this disease has been acquired. The measurement of circulating parathyroid hormone (PTH) by radioimmunoassay[2] made the diagnosis much easier. The use of newer assays for parathyroid hormone (midmolecule and immunoradiometric assays [IRMA] assays)[3] and for parathyroid hormone-related peptide (PTH-RP),[4] which is elaborated by some nonparathyroid cancers, has made the diagnosis of primary HPT more exact and the chance of misdiagnosis far less common. Localization studies of enlarged parathyroid glands have improved in recent years,[5] but problems of accuracy are still associated with their use. No single study in general use has been demonstrated to be more than about 80% accurate, and each procedure is associated with both false-positive and false-negative results of varying incidences.

In the face of these improvements, it is not surprising that changes in the philosophy and practice of parathyroidectomy have been suggested. Foremost among these is the use of unilateral neck exploration,[6,7] often guided by localization studies,[8] if the surgeon thinks that an adenoma is present on that side. This report surveys the potential strengths and weaknesses of this approach and compares it with bilateral neck exploration. Because a randomized study comparing these surgical approaches has not been performed, the following comments represent the opinions of the authors based on their personal experience and on a review of the literature. First of all, there is no substitute for experience. Although unilateral

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parathyroid exploration has been practiced with great success by experts such as Professors C. A. Wang[6] and Sten Tibblin,[7] the authors believe that the chance of failure when practiced by less sophisticated parathyroid surgeons *far outweighs* any potential benefit. The use of bilateral neck exploration with careful, judicious use of parathyroid biopsy of only one normal appearing gland when an adenoma is present[9] greatly decreases the chance of missing asymmetric hyperplasia or double adenomas, results in a low incidence of postoperative hypocalcemia, and gives superior results, especially for the less experienced parathyroid surgeon.

Historical Perspective

In 1925, the first parathyroidectomy was performed in Vienna[10] on "Albert," the now famous trolley car operator. Albert had developed severe bone disease, a condition that was thought by many pathologists at that time to be due to parathyroid insufficiency. Only after failure of injections of parathyroid extract and the failure of a parathyroid transplant was surgical excision considered. In 1925, a parathyroidectomy was performed by a young surgeon, Dr. Felix Mandl. One large gland was removed, and the operation resulted in symptomatic improvement of Albert's condition for about 6 years; then his bone problems recurred.[11]

The first patient who was operated on in the United States for primary hyperparathyroidism was a merchant marine captain, Charles Martell.[12] Over the years, Captain Martell had developed a debilitating bone disease, with severe pain, "brown tumors," fractures, and kyphoscoliosis. He was recognized to have hypercalcemia and hypophosphatemia. These blood abnormalities, it was noted, were similar to changes that occurred when parathyroid extract was given to children with chronic lead poisoning to mobilize lead from their bones. They too developed hypercalcemia and low circulating phosphate levels. Thus it was postulated that Martell had an overactivity of the parathyroid glands. Unaware of the successful parathyroidectomy in Vienna, doctors at Massachusetts General Hospital explored his neck in 1926.[13] Unfortunately, only normal structures were found. Five other unsuccessful neck operations were performed over the following years until, in 1933, a large parathyroid gland was found in his mediastinum. Ninety per cent of it was resected; the remaining part was intentionally left in place to try to prevent tetany. Despite this, as might be expected in a patient with very severe bone disease, postoperative tetany occurred. Six weeks later, Charles Martell died in chronic renal failure after an operation to remove a kidney stone that had blocked his ureter.

How ironic it seems that the first two patients who were operated on for primary hyperparathyroidism had serious difficulties associated with their surgical therapies. The same problems still concern us even today. Albert appears to have demonstrated *recurrent hyperparathyroidism.* Charles Martell had an *ectopic parathyroid adenoma* and required multiple neck operations with removal of most, if not all, of his normal parathyroid glands before it was found in his chest. Severe hypocalcemia, which was difficult to treat, followed removal of most of this mediastinal tumor.

Prevalence

Primary HPT is no longer an uncommon disease. In fact, it appears to be the most common cause of hypercalcemia in nonhospitalized patients. It occurs in about 1 in every 500 women over 40 years of age and in about 1 in every 2000 men.[5]

Symptoms

When first described, primary HPT was a disease of the bones. It soon became apparent, however, that kidney stones were more common than severe bone disease. Gradually other symptoms and signs were added to this syndrome, largely because of the work of Oliver Cope[14] and his associates (Table 1). Later, an increased incidence of chondrocalcinosis, pseudogout, and gout was recognized as well.

As medical students, we all learned that primary HPT is associated with "painful bones, renal stones, abdominal groans, and psychic moans." Today many other individuals are discovered to have this disorder because of the recognition of hypercalcemia on multiphasic chemical blood screening tests. Many of these patients are thought to be "asymptomatic" by their physicians. By this designation, many physicians mean that they have none of the classical symptoms and signs that are listed in Table 1. However, a careful history often discloses subtle or even profound symptoms of fatigue, weakness, depression,

TABLE 1. *Clues to the Diagnosis of Hyperparathyroidism in the First 343 Cases at the Massachusetts General Hospital*

Clue	No. of Cases
Renal stones	195
Bone disease	80
Peptic ulcer	27
Fatigue	10
Pancreatitis	9
Central nervous system signs	7
Hypertension	6
Mental disturbance	3
Multiple endocrine abnormalities	3
No symptoms (routine laboratory test)	2
Lump in neck	1

Reprinted with permission from Cope.[14]

polyuria, polydipsia, arthralgia, or constipation.[5] Further testing often shows an accelerated course of osteoporosis. Studies from Uppsala,[15] for example, have documented that alterations in neurotransmitter levels comparable to those found in endogenous depression are present in patients with primary HPT. These abnormalities, they have shown, revert to normal after successful parathyroidectomy. Thus, the definition of "asymptomatic" in patients with primary parathyroidism often differs according to "the eye of the beholder."

Diagnosis

To be successful, the clinician must diagnose those individuals who have primary hyperparathyroidism and distinguish them from the many others who have hypercalcemia of other causes (Table 2). The diagnosis of primary HPT is usually made by findings of elevated serum calcium levels associated with elevated parathyroid hormone concentrations. The newer assays for circulating parathyroid hormone have made the diagnosis of primary HPT much more secure. In our laboratory, an elevation of midmolecular PTH in patients with hypercalcemia has correlated very well with primary hyperparathyroidism. The newer, double-antibody IRMA assays[3] that measure intact PTH may be even more exact, for they are less influenced by the presence of renal failure or renal impairment. Using this new assay, it may be possible to measure changes in circulating PTH intraoperatively after removal of all abnormal parathyroid glands to assure that the operation has been curative. This procedure has not yet been perfected, however.

The importance of properly measured serum calcium values in the chemistry laboratory cannot be overemphasized. Sometimes hypercalcemia may be subtle, although symptoms such as repeated kidney stones may be severe. The better laboratories usually have upper levels of serum calcium concentrations of 10.3 mg/dL or less. In most such laboratories, the diagnosis of normocalcemic hyperparathyroidism is very uncommon. In cases of hypoproteinemia, an elevation of *ionized* calcium levels may be diagnostic of primary HPT in the face of normal total calcium levels.

TABLE 2. *Differential Diagnosis of Hypercalcemia*

- Malignancy
  - Solid tumors with or without bony metastases
  - Multiple myeloma
  - Lymphomas and leukemias
- Endocrine
  - Hyperparathyroidism
  - Hyper- and hypothyroidism
  - Addison's disease
  - VIPomas, pheochromocytoma
- Granulomatous disease
  - Sarcoidosis
  - Tuberculosis
- Increased intake
  - Calcium
  - Vitamin D and vitamin A intoxication
  - Milk alkali syndrome
- Miscellaneous
  - Benign familial hypocalciuric hypercalcemia
  - Paget's disease with immobilization
  - Thiazides
  - Lithium

Reprinted with permission from Clark and Duh.[5]

Serum phosphate levels are low in about 80% of cases. Alkaline phosphatase values are not often elevated, only when severe bone disease is present. In virtually all cases of primary HPT, the urinary calcium output is 200 mg/day or greater when the patient eats a standard diet. Values lower than these are suggestive of familial hypocalciuric hypercalcemia,[16] a condition that should not be treated surgically.

A list of the differential diagnoses of hypercalcemia is shown in Table 2. A detailed discussion of each disease state is beyond the scope of this paper. It should be observed, however, that although metastatic bone disease is the most common cause of hypercalcemia in hospitalized patients, primary HPT is the most common cause of hypercalcemia among outpatients[5] and is the second most common cause in the hospital setting. An uncommon but difficult problem in the past has been the fact that some tumors elaborate a PTH-like peptide that is thought to be the cause of hypercalcemia. A recently discovered peptide, PTH-RP,[4] can be measured in the blood of many such patients and can be used to differentiate them from others with primary HPT; thus inappropriate parathyroidectomy can be avoided.

Indications for Parathyroidectomy

The purpose of the parathyroidectomy in primary HPT is to restore the patient to a normocalcemic, euparathyroid state and to reverse the symptoms associated with this disease. With correction of the hyperparathyroid state, most but not all of the symptoms and signs of the disease are reversed[17,18] (Table 3). Bone disease (osteitis) is universally benefited. Roentgenographic evidence is seen of healing of bone cysts; the "salt and pepper" osteolysis of the skull, and subperiosteal bone resorption are corrected. Patients with nephrolithiasis develop far fewer new stones. Renal function also has been shown to improve in some studies, but not in all. Malaise, fatigue, weakness, and depression, often classified as neuropsychiatric symptoms, improve or disappear in as many as three fourths of patients. Up to half of all peptic ulcers will improve or heal. Uric acid levels decrease in many individuals. Nausea, polyuria, polydipsia, and constipation are frequently relieved. Only hypertension, seen in many patients with this disease, is not benefited in most patients with primary hyperparathyroidism.

TABLE 3. *Response of Symptoms and Signs to Parathyroid Surgery at 5-Year Follow-up*

	Preoperative Prevalence (%)		Long-term Improvement (%)	
Symptoms and Signs	Ronni-Sivula and Sivula (n = 289)	Lafferty and Hubay (n = 100)	Ronni-Sivula and Sivula (n = 289)	Lafferty and Hubay (n = 68)
Osteitis	4	6	100	100
Pancreatitis	2	3	100	100
Renal calculi	34	18	90	92
Neuropsychiatric*	61†	21	72	71
Constipation	14	15	63	70
Peptic ulcer	3	16	25	45
Hypertension	31	48	3	7
Impaired renal function	14	15	43	0
Asymptomatic	35	49	0	0

* Includes fatigue, lethargy, malaise, weakness, depression, headache, irritability, and confusion.

† Combines malaise, fatigue, and weakness in 46% plus depression in 15%.

Adapted from Lafferty and Hubay.[18]

Because of the success of parathyroidectomy, most clinicians believe that if a patient is symptomatic and is not a prohibitive medical risk, a parathyroidectomy should be performed. Some differences of opinion exist about the value of parathyroidectomy for patients who are asymptomatic. Scholz and Purnell[19] at the Mayo Clinic demonstrated, for example, that about half of the asymptomatic patients with clear hyperparathyroidism who could be successfully followed for 10 years developed some problem associated with their disease. They recommended parathyroidectomy in such patients because follow-up was difficult and the operation was very successful at their institution. Other studies have demonstrated the value of parathyroidectomy in patients with primary hyperparathyroidism and asymptomatic osteoporosis, as measured by bone densitometry.[20] Not all investigators agree, however.[18] Thus, the value of parathyroidectomy in truly asymptomatic patients is still being debated. All agree, however, that the most important prerequisite for success is an experienced parathyroid surgeon.

Pitfalls for the Surgeon

Difficulties associated with parathyroidectomy for primary HPT relate to the variability in the number of parathyroid glands, the different locations of normal and pathologic glands, and problems distinguishing normal glands from others that are subtly diseased. To be successful, a parathyroid surgeon must have an excellent knowledge of the anatomy, embryology, and pathophysiology of the parathyroid glands.

Number of Parathyroid Glands

Gilmour,[21] in an extensive autopsy study, found that roughly 80% of individuals had four glands, 6% had five, and 13% had three. Two glands or six glands were present very rarely. Other anatomists and surgeons have found more than six glands to be present in some cases. This variability creates difficulties for the surgeon in several situations. First of all, four normal glands may be present in the neck, whereas a fifth, a *supernumerary* gland, which is adenomatous, may be present in the mediastinum. This situation occurred in 5 of 14 mediastinal parathyroid adenomas that were reported from the Mayo Clinic prior to 1970,[22] for example.

A second example in which the number of glands plays an important role is in primary parathyroid hyperplasia. Particularly in the multiple endocrine neoplasia type 1 (MEN-1) or other familial syndromes, recurrent hyperparathyroidism occurs frequently, even after subtotal resection of parathyroid glands in the neck.[23,24] A thymectomy must be included as part of the standard parathyroidectomy for this condition to remove other parathyroid glands that might be present in this tissue.

Location of Parathyroid Glands

Embryology. The upper parathyroid glands arise embryologically from the dorsal part of the fourth branchial pouches, along with the lateral lobes of the thyroid, the ultimobranchial bodies[21,25] (Fig. 1). They descend only slightly during embryologic life along with the thyroid and continue to remain in close association with the upper portion of the lateral thyroid lobes. Because of their relatively circumscribed migration, their position in adult life remains quite constant.

The lower parathyroids arise from the dorsal part of the third branchial pouches along with the thymus and they descend with the thymus. Because they travel so far in embryologic life, they have a very wide range of distribution in the adult. They may be found all the way from just beneath the mandible anterior to the carotid artery bifurcation, to the pericardium (Fig. 2). When the

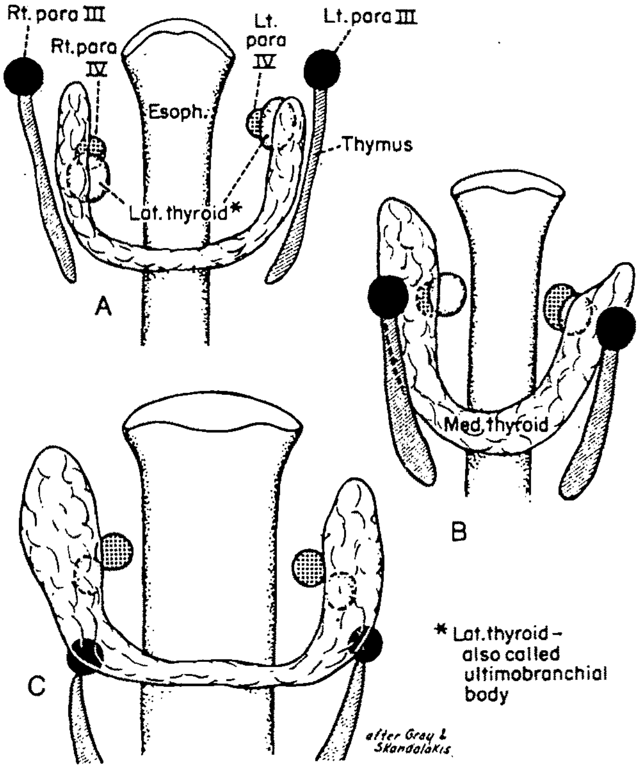

FIG. 1. (A and B) Schematic representation of the embryologic shifts in locations of the thyroid, parafollicular, and parathyroid tissues. (C) Approximate adult position. Reprinted with permission from Sedgwick and Cady.[25]

lower parathyroid gland descends into the mediastinum, it is almost always anterior to the recurrent laryngeal nerve.

Location of Normal Glands. The average weight of a normal parathyroid gland is 35 to 50 mg. Some may be slightly heavier. They can be thought of as being about half the size of one's little fingernail; thus they are small and they can be difficult to identify. Normal glands are usually yellowish-brown and sometimes look like fat, particularly to the inexperienced eye. They are also difficult to find because of their various possible locations.

In most cases, the normal upper gland may be found on the posterior portion of the middle third of the thyroid, usually toward the superior part of this area, either under a delicate fascia on the thyroid lobe or on a projecting nodule[21,26] (Fig. 3A, B). It usually is found cephalad to the inferior thyroid artery and close to the recurrent laryngeal nerve as it enters the larynx.

The normal inferior parathyroid glands are more variable[21] (Fig. 3A, B). In somewhat more than 50% of cases, the lower parathyroid is found on the lateral or posterior surface of the lower pole of the thyroid gland, or not more than 0.5 cm below the lower pole. The next most common location, in 12.8% of the cases, is within 1 cm below the lower pole of the thyroid. In most of the remaining individuals, the lower parathyroid gland is found within the tongue of the thymus (called the thyrothymic ligament). The tongue of the thymus usually can be identified just below the lower pole of the thyroid gland on each side, adjacent to the inferior thyroid veins. Less frequently, normal inferior parathyroids can be located in the superior mediastinum within the thymus. Finally, rarely they are found high in the neck, the so-called undescended parathyroid glands.

Gilmour[21] found that the parathyroids occasionally are included within the thyroid capsule or lie beneath it.

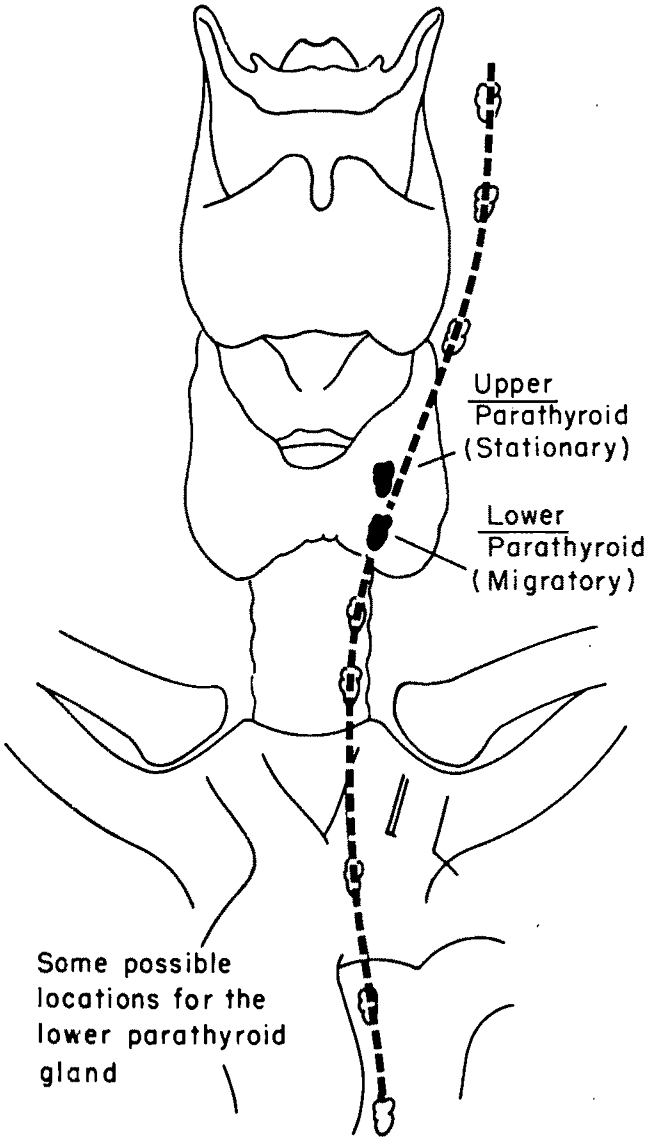
Upper Parathyroid (Stationary)
Lower Parathyroid (Migratory)
Some possible locations for the lower parathyroid gland

FIG. 2. Descent of the lower parathyroid. The upper parathyroid occupies a relatively constant position in relation to the middle or upper third of the lateral thyroid lobe, but the lower parathyroid normally migrates in embryonic life and may end up anywhere along the course of the dotted line. When this gland is in the chest, it is nearly always in the anterior mediastinum. Reprinted with permission from Kaplan.[26]

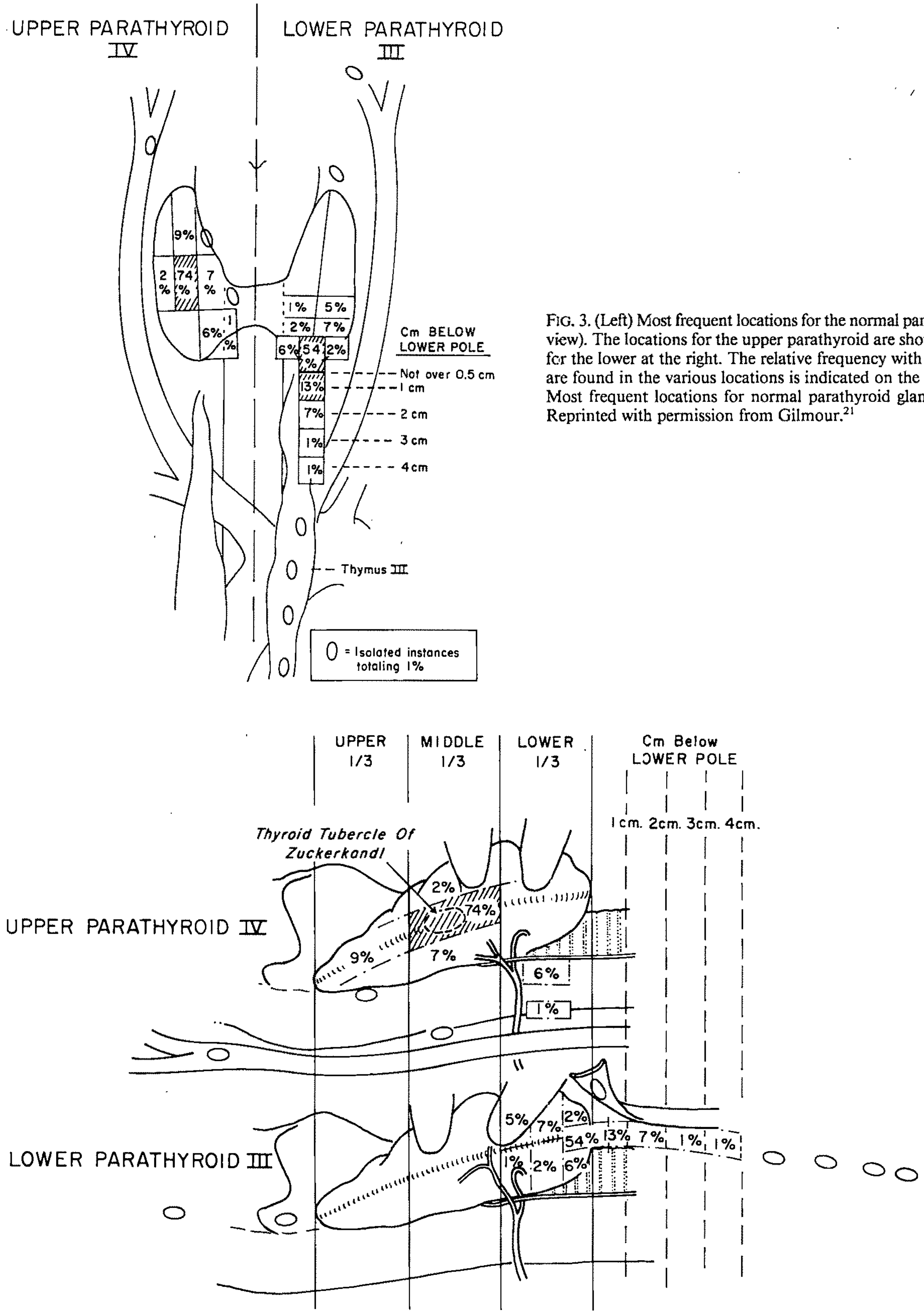

FIG. 3. (Left) Most frequent locations for the normal parathyroid (anterior view). The locations for the upper parathyroid are shown at the left and for the lower at the right. The relative frequency with which the glands are found in the various locations is indicated on the diagram. (Below) Most frequent locations for normal parathyroid glands (lateral view). Reprinted with permission from Gilmour.[21]

Sometimes, a parathyroid is completely covered by the thyroid. These intrathyroidal lesions usually involve the inferior parathyroid glands. Normal lower parathyroid glands are usually anterior to the recurrent laryngeal nerves, whereas the upper parathyroid glands are usually situated more posteriorly.

Abnormal Parathyroid Glands. When parathyroid glands enlarge and become adenomatous or hyperplastic, their position can change.[27] Large upper parathyroid glands frequently fall back, posterior to the recurrent laryngeal nerve and under the inferior thyroid artery, and are found along the esophagus down into the posterior-superior mediastinum. Lower parathyroid glands are displaced into the anterior-superior mediastinum, either separately or along with the thymus gland. Usually they remain anterior to the recurrent laryngeal nerves.

Although 80% to 85% of parathyroid adenomas are found adjacent to the thyroid gland in their normal locations, 15% to 20% are ectopically placed. Ectopic glands can be found in the anterior-superior mediastinum, either within or outside of the thymus, along the esophagus into the posterior-superior mediastinum, or very rarely in the middle mediastinum.[28] Uncommonly they can be found within the carotid sheath or even *lateral* to the carotid sheath.[29] Rarely, an "undescended" lower parathyroid gland is found high up in the neck, anterior to the carotid artery bifurcation. Finally, 3% to 5% of all parathyroid adenomas are intrathyroidal, usually within the lower pole of the thyroid gland. Fortunately, most of these can be felt or recognized as a mass within the thyroid lobe, but in other instances they are found only after thyroid excision or thyroidotomy. Locating and removing *ectopic* parathyroid glands during the initial neck operation remains one of the major pitfalls to successful parathyroid surgery.

Pathology of Primary Hyperparathyroidism

One of the most difficult aspects for the surgeon is the recognition of the pathologic process that is present, for appropriate treatment is dependent on this. Primary hyperparathyroidism may be due to a parathyroid adenoma, to hyperplasia of the parathyroid glands, or rarely to a parathyroid carcinoma. The symptoms of the disease are similar regardless of the actual cause.

Originally in the treatment of hyperparathyroidism, all patients were believed to have either single or multiple adenomas or water clear hyperplasia, the latter being a condition rarely if ever diagnosed today. Primary chief cell hyperplasia was not recognized as an entity until Cope and co-workers described it in 1958.[30] Hence, studies that include data from before this time are misleading, for multiple enlarged glands were usually called multiple adenomas instead of hyperplasia.

In the late 1960s and early 1970s, the difficulties of diagnosing mild chief cell hyperplasia pathologically became evident. As shown in Table 4, the prevalence of chief cell hyperplasia varied considerably in series from different institutions, from 3% to 65%. It was finally concluded that the pathologists were being greatly influenced by the operation that was performed.[31] When subtotal parathyroidectomy was performed routinely, more hyperplasia was diagnosed. When a more conservative operation was performed with removal of a single gland, it was most likely called an adenoma. The importance of mild hyperplasia and the best way of diagnosing this condition are questions that still are being debated.[32]

Today, however, it is generally agreed that primary HPT is caused by a single adenoma in 80% to 85% of cases and that chief cell hyperplasia is found in 15% to 20% of cases. In the MEN-1, MEN-2A and the familial hyperparathy-

TABLE 4. *Relative Frequency of Parathyroid Adenoma, Hyperplasia, and Carcinoma in Reported Series*

Author and Year	No. of Patients	Adenoma (%)	Primary Hyperplasia (%)	Carcinoma (%)
	300	96	3	1
Goldman et al., 1971	100	96	3	1
Krementz et al., 1971	788	93	6	1
Hoehn et al., 1969	350	90	7	3
Davies, 1974	250	90	9	<1
Palmer et al., 1975	307	90	10	
Myers, 1974	185	82	11	1
Werner et al., 1974	129	84	14	1
Wang, 1976	431	82	14	4
Romanus et al., 1973	274	81	19	—
Block et al., 1974	121	80	20	—
Bruining, 1971	242	60	40	—
Haff and Armstrong, 1974	35	57	43	—
Esselstyn et al., 1974	100	51	49	—
Haff and Balinger, 1971	74	50	50	—
Paloyan et al., 1973	84	33	65	—

Reprinted with permission.[26]

roidism syndromes, hyperplasia is the rule. Parathyroid cancer is found in less than 1% of cases in many series, including the authors' experience,[26] but makes up 3% to 5% of others. Perhaps it is being overdiagnosed in some institutions.

Classically, an adenoma has been defined pathologically as an enlarged gland with a rim of normal tissue. However, Roth[33] and other pathologists state that this histologic appearance can be found in cases of hyperplasia as well, and that *it is not possible to tell the difference between hyperplasia and adenoma from looking at only one gland;* other glands must be examined.

The greatest differences of opinion relate to what constitutes mild hyperplasia and whether or not mildly hyperplastic glands are of physiologic importance.[32] Some pathologists consider normal-sized or mildly enlarged glands to be hyperplastic if they do not contain enough extracellular fat. Others do not feel that such glands are necessarily abnormal, and consider the amount of *intracellular* fat to be the most important criterion in this differentiation.[34] Some pathologists use fat stains or osmium stains at the time of frozen section to evaluate intracytoplasmic fat in normal-appearing or mildly enlarged glands. However, the validity of these techniques has not been accepted by all pathologists, and they present some technical complexities as well. Many pathologists and surgeons believe that the differentiation of a mildly hyperplasic from a normal gland by frozen section examination is very difficult.

The major problem for the surgeon at the time of operation is to differentiate an adenoma from chief cell hyperplasia, or single gland disease from multiglandular disease of the parathyroids. In general, most experienced surgeons think that by evaluating the size, shape, and color of the parathyroid glands at operation, they can distinguish normal glands from abnormal ones. If one gland is enlarged and the others are perfectly normal visually and by biopsy with frozen section, this is an adenoma. If all glands are enlarged this is hyperplasia (or multiglandular disease).

A significant difficulty at the time of operation is that the glands of parathyroid hyperplasia may be *asymmetric;* not all of the glands exhibit the same degree of enlargement. Some, in fact, may appear normal or near normal. Bruining[27] has demonstrated that two and three gland enlargements were present in a number of his cases (Fig. 4) Each of these patients had one or more normal or near normal appearing glands. Most authors agree that double adenomas[24,35] occur in 5% or fewer cases; however, others believe that this represents a form of multiglandular disease. Thus, because the microscopic differentiation of an adenoma from hyperplasia is difficult when examining one enlarged gland and because frozen section differentiation of mild hyperplasia from normal is also very difficult, most surgeons believe that *they play the major role* as *diagnostician as well as therapist.* Obviously, the more glands the surgeon can see and evaluate, the more reliable will be the diagnosis and, hence, the treatment.

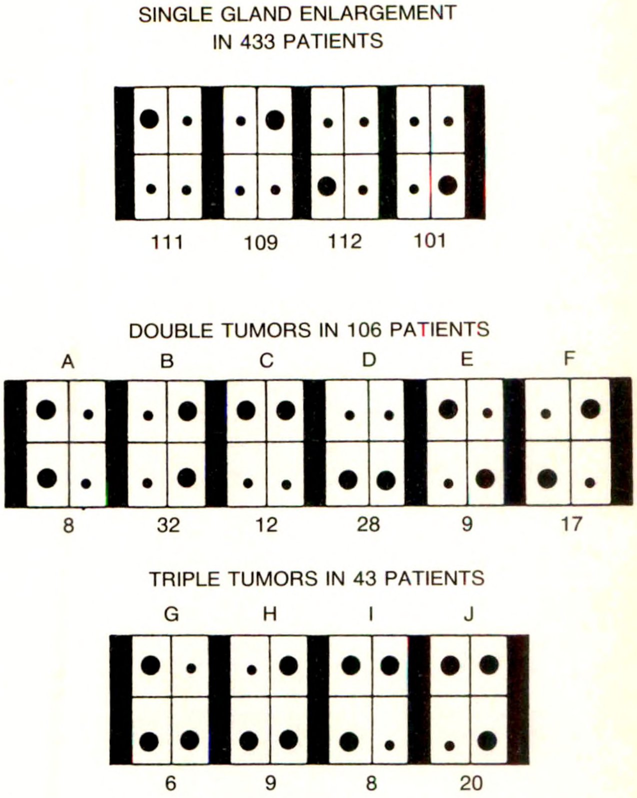

FIG. 4. Location of parathyroid tumors in a series of 582 patients. Reprinted with permission from Bruining.[27]

Localization Procedures

Clark and Duh[5] have written an excellent summary of the advances that have been made in the preoperative localization of parathyroid tumors. With experienced radiologists and modern equipment, about 75% to 80% of all parathyroid tumors can be localized using either ultrasonography, thallium-technetium scanning, magnetic resonance imaging (MRI) or computed tomography (CT). In the best studies, using multiple techniques, as many as 80% to 90% of single parathyroid tumors have been identified.

In every series, however, both false-positive and false-negative results have been obtained. The tests are best when a single parathyroid gland enlargement is present, when the tumor is larger than 1 g in weight, and when no thyroid nodules are present. Only 20% of multiple gland enlargements are correctly identified. Thus, localization studies of patients with hyperplasia can be very misleading. Other problems relate to the small size of many parathyroid tumors, their position deep in the neck or chest, and the fact that thyroid nodules are frequently present, especially in elderly female patients, the very individuals who have the highest prevalence of primary hyperparathyroidism.

Ultrasonography is very *operator dependent.* Although experts may localize 80% or more correctly, others with less experience correctly localize far less than half.[8] This technique is good only in the neck, and is best when a 10-mHz real-time, small parts scanner is used. It usually cannot identify small lesions, especially those deep in the neck or behind the esophagus. It cannot be used for lesions under the sternum. In some centers, needle aspiration of the suspected tumor is performed under ultrasound guidance. Cytologic examination and parathyroid hormone measurement of the aspirate may add to the certainty of the findings. The appearance of an intrathyroidal parathyroid on ultrasonography is shown in Figure 5.

Thallium-technetium scanning, although done in many hospitals, is very difficult to do well. Thallium (^{201}Tl) is taken up by both the thyroid and by enlarged parathyroid glands, whereas technetium (^{99m}Tc) pertechnetate is taken up only by the thyroid. Images with each isotope are obtained and then the technetium scan is subtracted from the thallium scan by computer analysis. What remains is the image of the enlarged parathyroid gland.

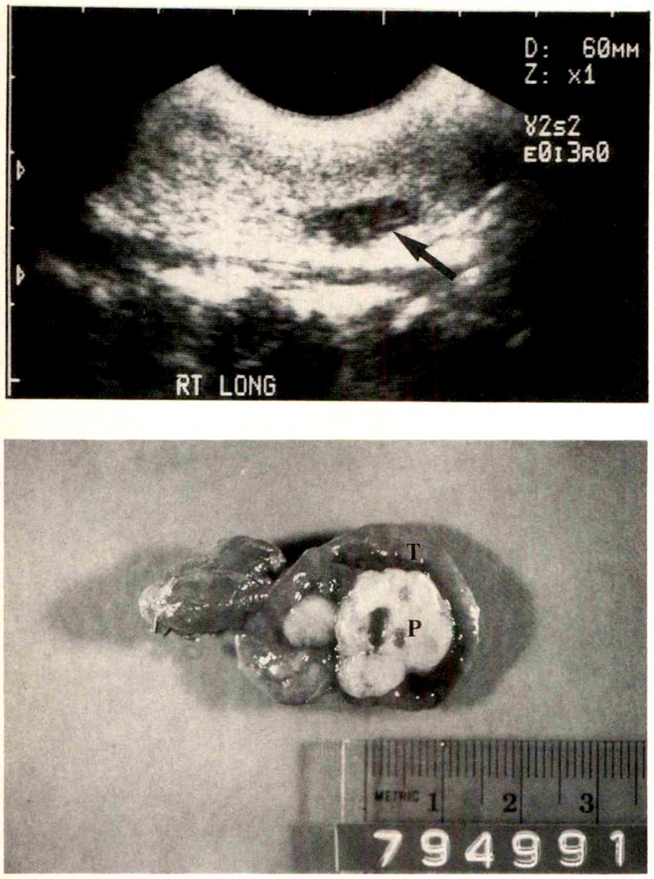

FIG. 5. Intrathyroidal parathyroid adenoma. (Top) Visualized preoperatively within the right thyroid lobe by sonography. The parathyroid adenoma (arrow) appears hypoechoic relative to the surrounding thyroid tissue. Courtesy of Dr. David Yousefzadeh. (Bottom) Gross appearance of a different intrathyroidal parathyroid adenoma. T, thyroid; P, parathyroid adenoma.

Potential problems with this technique create false-positive results in 10% to 20% of the cases. The patient must not move; for this reason we use a harness. Thyroid nodules interfere with the subtraction procedure. We have found, however, that this scan, when done well, is excellent for imaging ectopic parathyroid glands, those *away* from the thyroid gland (Figs. 6 and 7).

Although we have used CT examinations less frequently, these can be of value especially for mediastinal, substernal tumors (Figs. 7 and 8). Magnetic resonance imaging examinations do not require contrast material, and parathyroid tumors are usually bright on T2-weighted imaging (Fig. 9). In our experience, small tumor size, movement of the carotid arteries, and technical difficulties associated with the lower neck and upper chest make MRI examination less rewarding.

Venous catheterization with blood sampling for parathyroid hormone has largely been replaced by the other modalities; however, it still plays a role in lateralizing the side of the disease in very difficult cases. Arteriography is rarely done in our experience because of the potential for severe complications. Finally, we have not found toluidine blue or methylene blue used intraoperatively to be of value.

To Localize or Not To Localize

There is no question that localization studies should be used before all reoperative parathyroidectomies, or when one is contemplating parathyroidectomy in a patient who has had extensive thyroid surgery in the past (Fig. 10). This latter situation is not uncommon, because low-dose radiation to the neck is known to be followed by an increased incidence of both thyroid cancer and primary HPT.[36,37] The mean latency period for development of the hyperparathyroidism is longer than for thyroid cancer, so that a number of individuals who have had total or near-total thyroidectomy may later need a parathyroidectomy. Correct localization of the enlarged parathyroid gland before reoperative parathyroidectomy, as reported by Levin and Clark,[38] was between 45% and 68% for the various tests. Combinations of tests were better. Thus, although not perfect, localization studies greatly aid the surgeon and are mandatory before reoperative surgery.

When operating in the "virgin neck," most surgeons agree that there is no need to do localization studies. Common localization studies are about 75% to 80% accurate when done well. Because virtually all expert parathyroid surgeons cure 95% or more of such patients although they have not had localization studies, one could

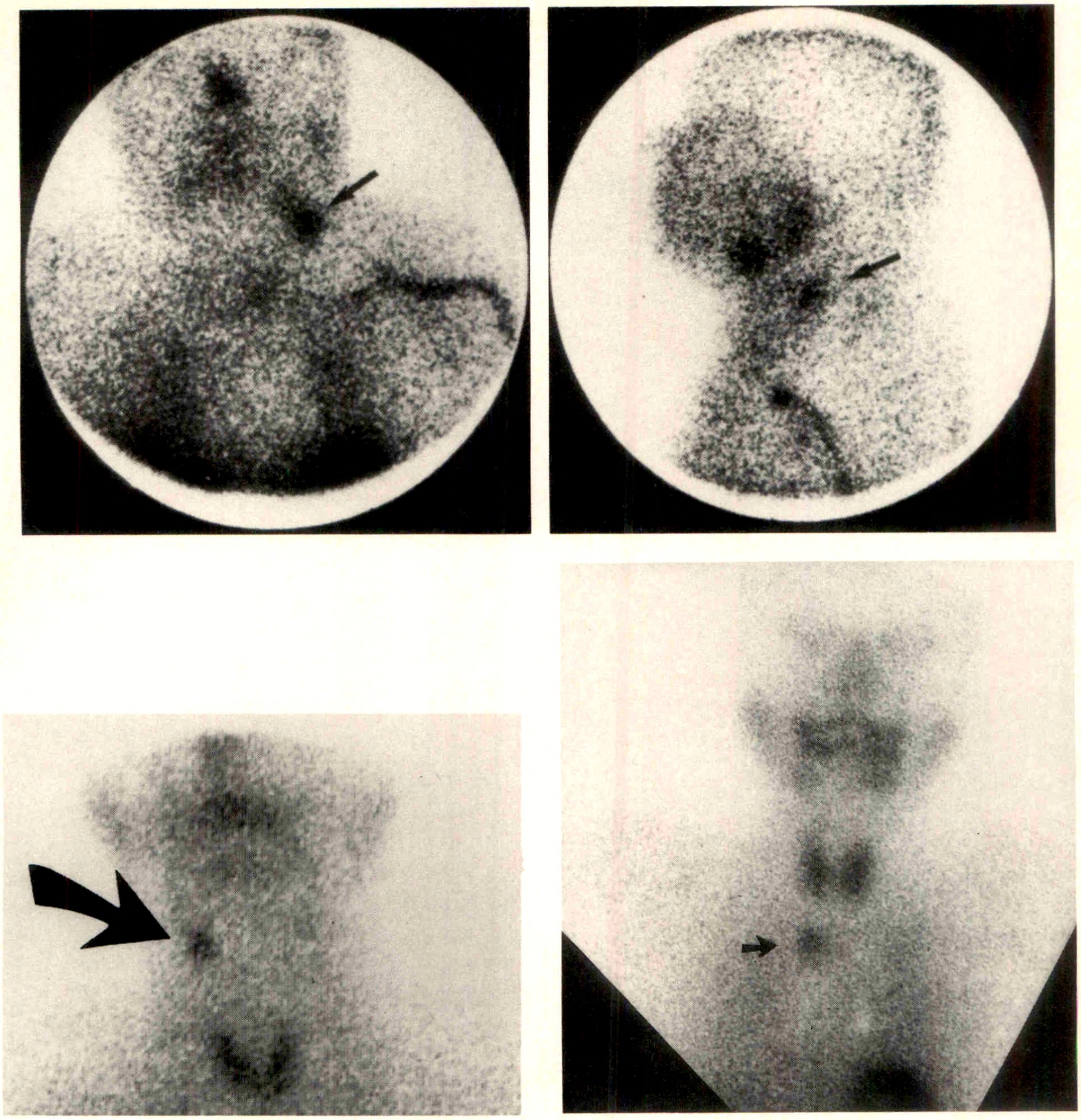

FIG. 6. Localization of ectopic parathyroid adenomas by thallium–technetium scanning. (Top) Adenoma of the left neck lateral to the carotid sheath (arrow), anterior (left) and lateral (right) views of the neck. Reprinted with permission from Udekwu et al.[29] (Bottom left) Undescended right lower parathyroid adenoma (arrow) located at the carotid bifurcation. The thyroid gland is seen clearly inferior to the adenoma. (Bottom right) Intrathymic parathyroid adenoma (arrow), seen inferior to the thyroid gland and superior to the heart. Courtesy of Drs. James Ryan, William Martin, and Malcolm Cooper.

argue that *the best localization procedure is to find an excellent parathyroid surgeon.* Furthermore, it has not been demonstrated uniformly that localization tests save time intraoperatively. Finally, the cost of both an ultrasound and a thallium-technetium scan at our institution is nearly $1100.00. On the other hand, by doing ultrasound preoperatively, a small number of intrathyroidal parathyroid adenomas may be localized, whereas a thallium-technetium scan may recognize the occasional "ectopic" gland. We use these studies especially in cases of hyperparathyroid crisis, for example. Thus, although not cost effective, preoperative localization tests may help a small number of patients.

There is a potential down-side, however, to the routine use of preoperative localization testing in patients who have not previously had surgery. Apparent localization of

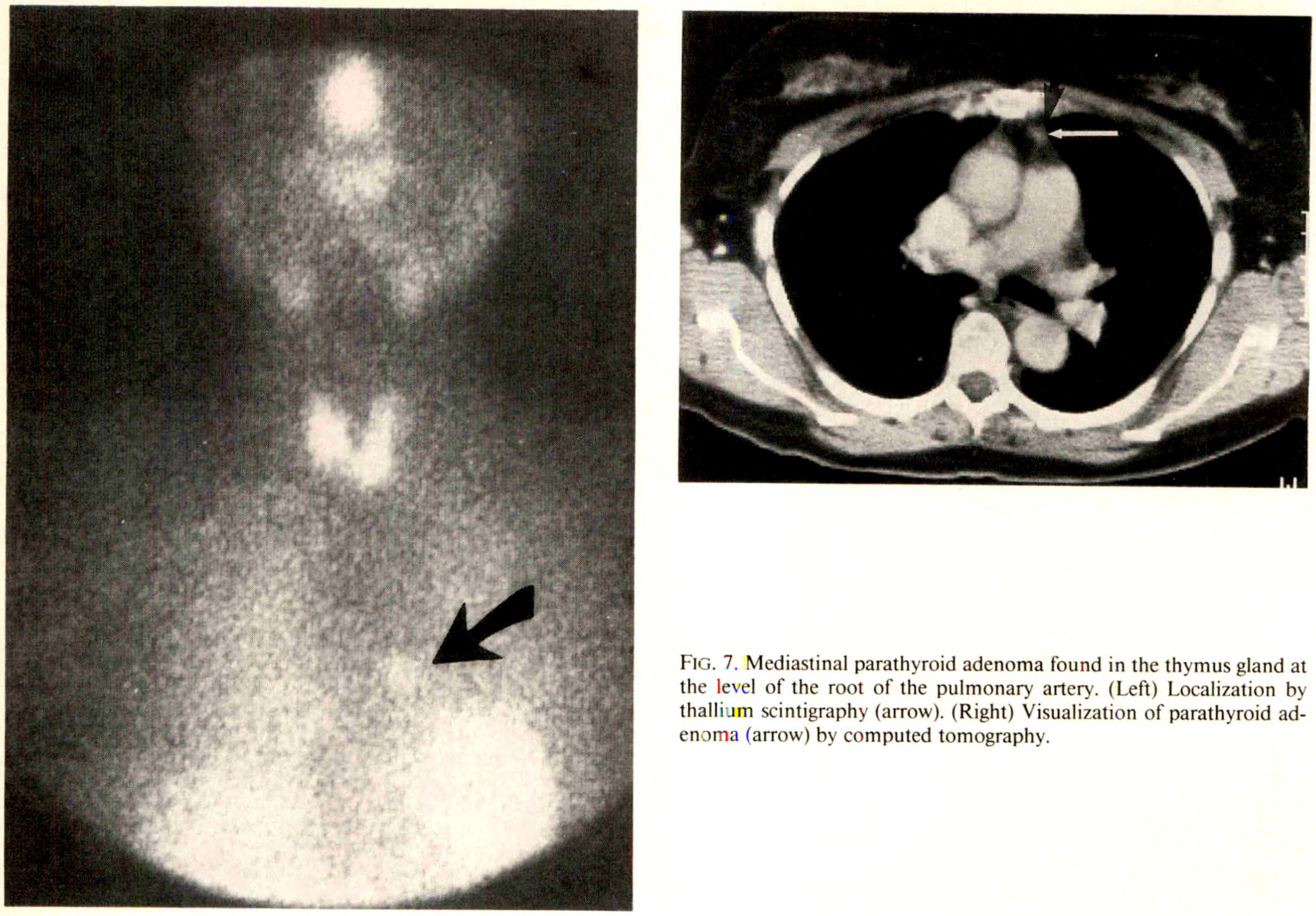

FIG. 7. Mediastinal parathyroid adenoma found in the thymus gland at the level of the root of the pulmonary artery. (Left) Localization by thallium scintigraphy (arrow). (Right) Visualization of parathyroid adenoma (arrow) by computed tomography.

one enlarged gland may serve as an invitation for the inexperienced surgeon to venture into the neck to remove that gland, perhaps not realizing that hyperplasia may be present. Remember that multiglandular disease is missed by localization studies in 80% of cases.[38] The first exploration is the best time to cure the hyperparathyroid state; the second parathyroidectomy is always much more difficult and less successful than the first.

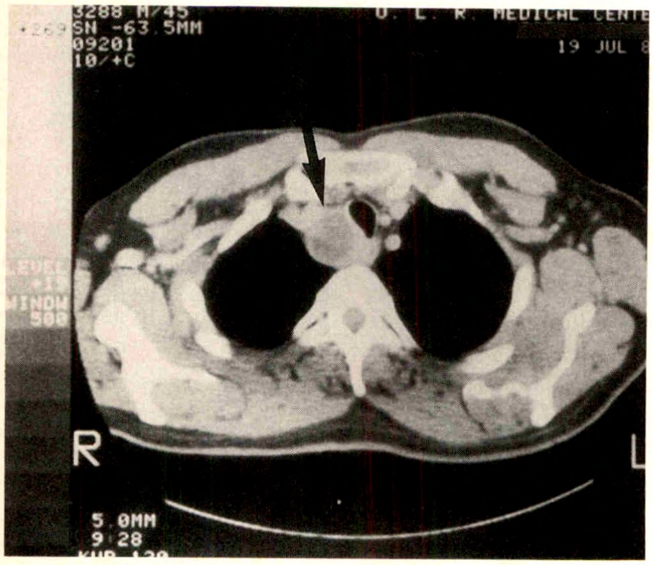

FIG. 8. Cystic mediastinal parathyroid adenoma (arrow) causing tracheal compression as seen by computed tomography.

Strategy of the Initial Parathyroid Exploration

The role of the surgeon in the first parathyroid exploration is to remove the offending gland or glands and thus cure the disease, or to assure himself or herself that no abnormal parathyroid tissue remains in the neck or in any ectopic location that might be reached by this exposure at the conclusion of a negative exploration.

Subtotal Parathyroidectomy

In the early 1970s, the incidence of parathyroid hyperplasia was found to be very high in a number of series.[26] Paloyan and Pickleman[39] proposed that correction of this condition required *subtotal parathyroidectomy* for all patients if persistent and recurrent hyperparathyroidism were to be prevented. Although this operation could be performed with very low morbidity rate by many of its proponents, in the hands of other surgeons, perhaps those less experienced, it resulted in a higher incidence of post-

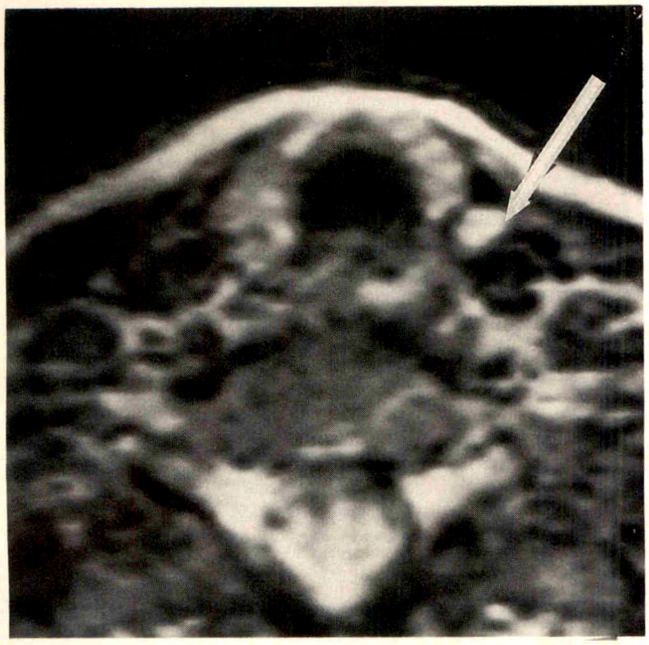

FIG. 9. Left cervical parathyroid adenoma (arrow) located by magnetic resonance imaging. This lesion is bright on T2-weighted imaging.

operative hypoparathyroidism. The subsequent use of *cryopreservation* of parathyroid tissue with the possibility of later reimplantation,[40] and the use of *autotransplantation* of parathyroid tissue at the time of the initial operation,[41] have greatly diminished this problem. Perhaps as a reaction to the proposal that all patients require subtotal parathyroidectomy, however, other operations were proposed or reexamined.

Unilateral Neck Exploration for Adenoma

Unilateral neck exploration is now practiced in 17% of the major parathyroid centers around the world, but mostly in Scandinavia and other European centers.[42] Wang[6] and Tibblin et al.[7] have long advocated that only one side of the neck be explored when an adenoma and a normal gland are found on the same side. These surgeons have considerable experience, and in their hands, the results of operation are excellent. They contend that the unilateral approach reduces operating time and hence, patient costs. Furthermore, they believe that the morbidity rate (recurrent laryngeal nerve injuries and postoperative hypoparathyroidism) is lessened, and the results of parathyroidectomy are just as good as with bilateral exploration. Reoperation, they believe, is not a problem, because the second side was untouched.

Wang[43] recently presented data that demonstrated that he performed a unilateral exploration in 70% of 800 first-time parathyroid explorations for adenoma. In these operations, he had a 4% failure rate. In 30% of the time

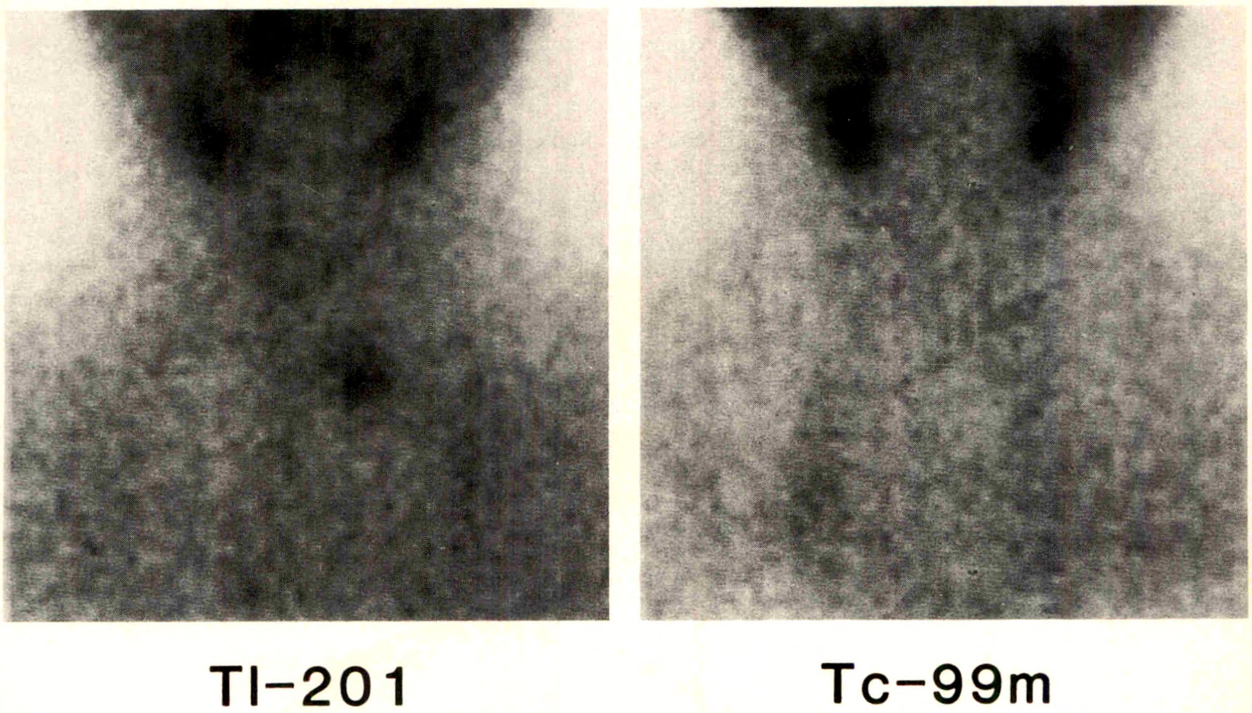

FIG. 10. Thallium-technetium scan of a 40-year-old man who underwent low-dose radiation therapy for tonsillitis as a child. At age 35, he was found to have papillary thyroid cancer and underwent a curative total thyroidectomy followed by radioiodine therapy. Five years later, primary hyperparathyroidism was diagnosed. On technetium scanning (right), no uptake is seen, signifying the absence of a thyroid gland. On thallium imaging (left), the parathyroid adenoma is visualized on the left side of the trachea. Reprinted with permission from Kadowaki et al.[47]

when an adenoma was present, (262 of 800 cases), he performed a bilateral operation, either because he explored the wrong side first, because the second gland on the ipsilateral side could not be identified, or because the adenoma was in an ectopic position. Six per cent of these 262 patients had persistent hyperparathyroidism, largely due to ectopic parathyroid adenomas in the mediastinum. This is clearly a superb series. If one adds the patients who had hyperplasia to the 30% who required exploration of both sides for adenoma, however, it should be noted that, in as many as 50% of all cases of primary HPT, Professor Wang performs a bilateral neck exploration.

Potential problems exist with unilateral neck explorations. These include *failure to recognize hyperplasia.* As shown in Figure 4, hyperplasia often may be asymmetric. The second gland might look very normal to the surgeon, especially to an inexperienced surgeon. The surgeon has only one gland other than the large one to evaluate and thus could easily misinterpret it. Wang proposes the use of a "gradient solution" in which a normal gland floats and a hyperplastic gland sinks. Tibblin et al.[42] emphasize the use of fat stains during frozen section. There also may be a failure to recognize *double adenomas,* a setting in which the two other glands are perfectly normal. These occur in 2% to 5% of cases in some series[24,35] and in 9% of patients over 65 years of age in the Michigan series.[35] Both hyperplasia and cases of double adenoma are much easier to diagnose, opponents argue, if both sides are examined. It has been estimated that exploration of the second side adds only 12 to 20 minutes of operating time. Finally, the practice of using localization studies to determine the side of the enlarged gland followed by unilateral exploration on this basis[8] may lead to increased numbers of patients with persistent or recurrent hyperparathyroidism, for localization tests only recognize 20% of the cases of hyperplasia.[5]

Thus, there are potential dangers for those who use this technique, especially for the inexperienced surgeon. We tell our residents that when they are as experienced as Professors Wang and Tibblin, they may use a unilateral approach. Until then, they and we should look at both sides of the neck.

Bilateral Operations

In a recent survey, 83% of major centers performing parathyroidectomies for primary HPT reported that they use a bilateral neck exploration.[42] This, they believe, permits a better assessment of the pathologic process that is present.

Initial Neck Exploration—The Authors' Approach

All surgeons agree that a parathyroidectomy should be performed in an unhurried, careful, delicate way. The operative field should be kept as blood free as possible. At the University of Chicago Medical Center, a bilateral operation has been the rule. If one gland is enlarged and the others are normal, this is an adenoma. In the last 10 years, our operative approach for adenoma has changed. In the late 1970s, our aim was to search for all normal glands when an adenoma was present and to carefully perform biopsies on each of them. This technique was modified in the early 1980s, when we demonstrated that a lesser degree of transient postoperative hypocalcemia occurred when all normal glands were visualized but when biopsies were done on only one or two of them.[9] We continue to be very pleased with this "middle ground approach," which was favored by two thirds of North American parathyroid centers in a recent survey.[42] In recent years we have performed biopsies on fewer normal glands.

If four glands are found to be enlarged, this is hyperplasia. In such cases, at least a subtotal parathyroidectomy is necessary. Three glands and part of the fourth are excised, leaving a well-vascularized remnant of about 50 mg tissue. Each thymic tongue also should be excised routinely as part of this procedure, to be certain that supernumerary parathyroid glands are not present. The partial resection of the parathyroid gland that is to be left always should be performed first, so that one can see that the remnant remains well vascularized before removing the other three glands. In cases of *familial hyperparathyroidism or the MEN-1 syndrome,* one should strongly consider doing a total parathyroidectomy with an autotransplant of parathyroid tissue to the arm, as recommended by Wells et al.[44] This technique is advantageous because it is known that recurrent hyperparathyroidism occurs with some frequency, especially in patients with these familial, genetically induced syndromes.[23,24] If graft-dependent hyperparathyroidism recurs in the arm, this area can be explored under local anesthesia without the risk of a recurrent nerve injury, as would occur if the neck were re-explored. Wells et al.[44] recommend this approach for all cases of hyperplasia, familial and otherwise.

So-called *double adenomas* occur in a nonfamilial setting when two glands are enlarged and two others appear perfectly normal, grossly and histologically. This multiglandular disease is curable by removal of both enlarged parathyroid glands and biopsy of the two normal ones.

Search for Ectopic Parathyroid Glands

If an adenoma cannot be found in the usual locations at exploration, each normal parathyroid gland should be explored by biopsy and marked, and after positive identification as parathyroid tissue on frozen section, a diagram should be made of its location for later reference. Do *not* remove normal parathyroid glands; this complicates the situation when the adenoma is ultimately found. If three normal parathyroid glands are found and the fourth cannot be located, the surgeon should assess whether an upper or a lower parathyroid gland on that side is missing.

Very frequently, it is an adenoma of the *upper* parathyroid gland that is overlooked. This may be found posterior to the esophagus, or it often falls down along the esophagus into the posterior-superior mediastinum. The mistake in this situation is that the dissection was not carried out deeply enough, back to the prevertebral fascia of the neck. When this is done near the upper pole of the thyroid, a finger can be inserted safely behind the inferior thyroid artery and posterior to the recurrent laryngeal nerve. In many instances, an adenoma is palpable beside or behind the esophagus, and this gland can be pulled up and easily removed.

If the missing gland is the *lower* parathyroid gland, as much of the thymus as possible should be pulled up into the neck and resected, because the inferior adenoma often is found within the thymus. If the adenoma still cannot be found, the dissection should be carried up in a cephalad direction to the hyoid bone, where occasionally an "undescended" lower parathyroid adenoma is found anterior to the carotid artery bifurcation. If this is still nonrewarding, the carotid sheath should be opened from the level of the clavicle upward. Occasionally, a parathyroid adenoma will be found, which cannot be palpated, because it is flattened out like a pancake. The area of the neck lateral to the jugular vein also should be explored, for we have identified two patients who had a parathyroid adenoma in this unusual location.[29] Finally, the thyroid lobe on the side of the missing gland should be carefully palpated. Any lump within the thyroid should be excised, for this might represent an intrathyroidal parathyroid adenoma. Even if no lump is present, a "blind" subtotal resection of the thyroid lobe on the side of the missing gland should be performed. Sometimes a nonpalpable parathyroid adenoma will emerge. Others use a thyroidotomy and incise the lower pole of the thyroid rather than resecting it.

Remember that even if four normal glands are found in the neck, the surgeon should search all of these ectopic sites for a fifth gland that is adenomatous. Similarly, if four hyperplastic glands are found, these same sites should be explored because supernumerary glands may be present.

Only rarely should a sternotomy and formal mediastinal dissection be done as part of the first exploration. This procedure is probably indicated only if the patient is extremely ill from hypercalcemia that cannot be adequately managed medically. The reasons for this approach are several. First of all, rarely the diagnosis of hyperparathyroidism might be in error. Second, occasionally hypercalcemia regresses or is eliminated by the first neck exploration, despite the fact that no abnormal parathyroid tissue has been removed. This probably occurs when an adenoma is infarcted by accidental ligation of its arterial supply. Finally, it is well known that in almost all cases of persistent hyperparathyroidism, the offending gland or glands can later be removed through a neck incision, particularly if the first surgeon is not very experienced in this area. This approach is clearly illustrated in the Mayo Clinic series[22] in which, until 1970, 1000 parathyroid explorations were performed and only 12 required a sternotomy, an incidence of 1.2%. At the Massachusetts General Hospital,[45] 21% of cases of primary hyperparathyroidism involved ectopically placed parathyroid adenomas. Almost all of these, however, could be removed through a neck incision. Thus, *do not rush to do a sternotomy* as part of the first operation.

Reoperation for Persistent or Recurrent Hyperparathyroidism

Before reoperating, a number of factors that should be considered[46]:

1. Be certain that the patient has primary hyperparathyroidism and not some other hypercalcemic state.
2. Be certain that the severity of the hyperparathyroid state warrants the risk of reoperative surgery.
3. Be certain that the patient does not have familial hypocalciuric hypercalcemia. If so, do not reoperate. Such patients are cured of hypercalcemia only by total parathyroidectomy and they usually have few complications of their disease state.
4. Carefully read the previous operative note and pathology report and understand how many normal or abnormal parathyroid glands on each side were identified histologically and how many of them were removed. Review the pathologic slides if at all possible. Is this a case of a missing adenoma, incompletely treated hyperplasia, or even a recurrence of a carcinoma?
5. Use localization studies extensively.

Strategy and Technique

Reoperations of the neck are more difficult because of the scarring, changes in anatomy, and loss of tissue planes that occur as a result of the first exploration, whether it was for a thyroid or a parathyroid disorder.[46–48,54] Frequently, for example, the strap muscles will be densely adherent to the anterior surface of the thyroid lobes, making entry into the usual anatomic planes more difficult. Furthermore, the recurrent laryngeal nerve is in greater jeopardy because it may be encased in scar tissue, but especially because it might lie immediately beneath the strap muscles if the thyroid lobe was previously removed. Always evaluate vocal cord function preoperatively in such cases. Finally, because one's knowledge of how many viable parathyroid glands remain in the neck after the first exploration is often limited, the chance of creating permanent hypoparathyroidism after removal of one or more abnormal parathyroid glands found at re-exploration is increased.

Usually there is not a rush to reoperate, and it is better to allow some time to pass to permit the wound to heal, to re-evaluate the diagnosis, to perform localization testing, and to assess the findings of the previous operation. The location of parathyroid adenomas that were removed by Wang[48] at reoperation are shown in Figure 11.

When reoperating, we almost always explore the neck again first, unless an adenoma is localized to the mediastinum or to another ectopic site preoperatively. When an experienced parathyroid surgeon did the initial operation and was "certain" that the lesion was not in the neck, it is much more likely to be found in an unusual location.

The prior transverse neck incision is used and subplatysmal flaps are elevated. The strap muscles are often adherent to the thyroid lobes; hence, instead of separating them in the midline, it is often easier to use a "lateral approach, as described by Fiend,"[26] and to dissect the vertical plane between the sternocleidomastoid muscle and the strap muscles (Fig. 12). Not infrequently, this plane is totally unscarred, and by retracting the carotid sheath laterally and the thyroid gland medially, a "fresh" area containing the recurrent laryngeal nerve and parathyroid glands sometimes will be entered. If this area is scarred, the dissection should be started as low in the neck as possible, because this region is often untouched. Once the recurrent nerve is identified, it can be safely followed in a cephalad direction. If the adenoma was not localized beforehand, a bilateral neck exploration may be necessary if it can be done safely. In the case of either positive localization or retrospective determination of the side of the neck of the missing gland, the cervical dissection might be started there initially and might be unilateral if an adenoma is found or if the dissection is technically very difficult.

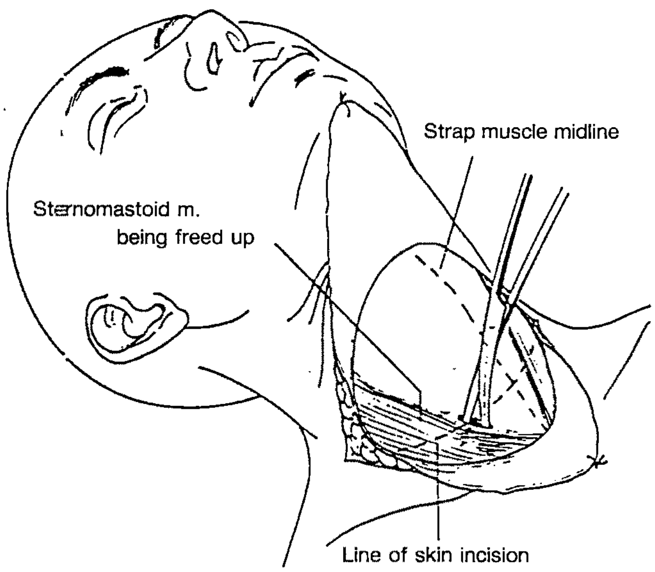

FIG. 12. During reoperative parathyroid operations, the strap muscles are often fixed to the surface of the thyroid lobes, making their usual mobilization difficult. Hence, rather than dissecting the midline, it is often easier to enter the plane between the strap muscles and the sternocleidomastoid muscle, an area that is often unscarred and allows easy access to the recurrent laryngeal nerve and to the parathyroid glands. Adapted from Kaplan.[26]

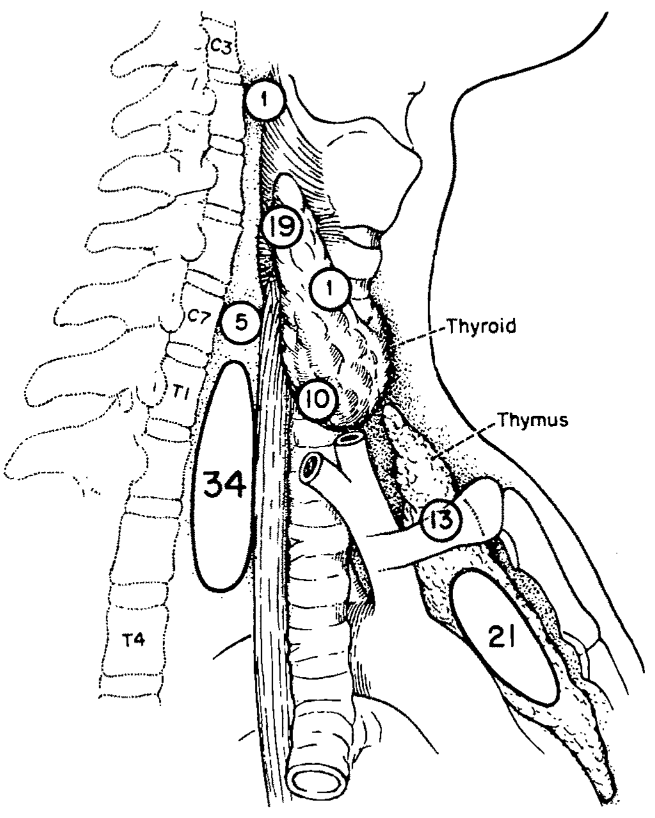

FIG. 11. Location of all parathyroid adenomas found at reoperation after failure to cure hyperparathyroidism initially, as described by Wang.[48] Note that most of these glands could be removed through a neck incision.

One of the most rewarding maneuvers, one that should be done early, is to look for an upper parathyroid gland that has fallen down into the posterior superior mediastinum. Introduce one's finger downward behind the inferior thyroid artery along the esophagus into the posterior mediastinum as far as one can reach. Often the missing adenoma can be palpated here before it can be seen. This is the area in which many missing adenomas are found because the initial dissection was not carried out deep enough.

If this is unsuccessful, all of the sites already described under the heading The Search for Ectopic Parathyroid Glands should be explored.[38] This involves pulling up and removing the thymus on each side into the neck, dissecting as high in the neck as the hyoid bone, removing a part of one or both thyroid lobes, and opening and exploring the carotid sheath areas and even lateral to the carotid sheath. A careful neck re-exploration done in this manner will almost always yield the missing adenoma or the elusive hyperplastic gland or glands that remain.

Before the operation, consent should be obtained for a possible sternotomy, if that is your plan. Either a partial sternotomy to the third intercostal space or a complete sternotomy can be performed. First, the thymus and surrounding fat pads should be palpated. On several occasions, we were able to feel a mass, which proved to be the missing adenoma, and only a partial thymectomy was necessary. Otherwise, the entire thymus should be removed. If the parathyroid gland is not found therein, a posterior dissection then should be performed. Lesions have been found between the aorta and pulmonary artery, in the middle mediastinum,[28] and even, very rarely, in an intrapericardial location.[22] Needless to say, these dissections can be very long and tedious.

When an adenoma is found in the neck or chest, it should be totally removed. If at least one additional normal gland remains viable after the first operation, the patient will be normocalcemic with normal postoperative parathyroid function. This fact stresses the importance of *not* removing normal parathyroid glands during an unsuccessful initial operation.

If hyperplastic glands are identified at reoperation, a subtotal parathyroidectomy can be performed. Others prefer a total parathyroidectomy, arguing that if recurrence were to occur in a remnant that is left, this would necessitate a third neck operation. If total parathyroidectomy is used, or after removal of an adenoma when one thinks that no other parathyroid tissue remains, one has the option of either immediately autotransplanting some of the abnormal parathyroid to the arm after confirming that it is not a carcinoma,[41] or else cryopreserving the tissue and waiting to see whether or not hypocalcemia occurs postoperatively.[40] If permanent hypoparathyroidism occurs, a subsequent autotransplant to the arm would be employed.

Either of these approaches has advantages and disadvantages. In our hands, cryopreservation has not been developed to the extent described by Wells et al.[40] and Brennan et al.[49] Furthermore, reimplantation of tissue that has been cryopreserved is not always successful. Hence we would be more likely to use immediate autotransplantation if it were thought to be necessary, but only if we believed strongly that *all* other parathyroid tissue had been removed from the patient. The long-term prevalence of recurrent hyperparathyroidism when part of an adenoma or of a hyperplastic gland is used as an autotransplant to the arm remains a fruitful area for study.

Surgery for Parathyroid Cancer

Parathyroid cancer accounts for less than 1% of cases of primary HPT at the University of Chicago Medical Center and elsewhere, but has been reported to occur in up to 6% of cases in other series.[50] A carcinoma often presents as a "sticky," adherent gland at operation. Often a thick, dense, fibrotic, whitish capsule is present.

If recognized or suspected intraoperatively, one should not enter its capsule, for local seeding of tumor is a common occurrence. The gland should be removed widely, taking the ipsilateral thyroid lobe with it. Ipsilateral lymph nodes should be dissected in the central compartment and perhaps in the lateral neck as well, for nodal spread can occur. Distant spread occurs to the lungs, bone, brain, and elsewhere. If hypercalcemia recurs after any parathyroidectomy for parathyroid carcinoma, metastases should be aggressively localized and resected,[51] because there is no good therapy other than surgical excision. In general, death occurs from unrelenting hyperparathyroidism with all of the complications of this disorder, rather than from tumor spread itself.

Results of Parathyroidectomy for Primary Hyperparathyroidism

There is no question that the results of parathyroidectomy for primary hyperparathyroidism relate to the experience of the operator. In a recent report from Scandinavia,[52] this is clearly shown. In centers that specialize in endocrine surgery, 90% of patients were normocalcemic, with mean follow-up of 4.4 years after their initial parathyroidectomy—6% were hypercalcemic and 4% were hypocalcemic. In contrast, in a general Scandinavian survey of all hospitals done at roughly the same time and with similar follow-up, 76% of patients were normocalcemic. In hospitals in which less than 10 operations for primary hyperparathyroidism were done each year, only 70% were normocalcemic at follow-up—15% had persistent or recurrent hyperparathyroidism and 14% had permanent hypoparathyroidism.

In a number of other studies from centers that have considerable experience in parathyroid surgery, approximately 95% of patients or more can be rendered normocalcemic by the initial operation.[23,27,53] At the University of Chicago, for example, over 97% of the last 300 patients who had their initial exploration at our Institution were normocalcemic, 1 month or longer after operation. Recurrent hyperparathyroidism occurs infrequently in nonfamilial cases,[18,23] but remains a problem in familial hyperparathyroidism and in others with the MEN-1 syndrome.[23] In experienced hands, the complication rate is low in these initial operations. Permanent recurrent laryngeal nerve injuries occurred in less than 1%.[18,52] Permanent hypoparathyroidism has been reported to be 2% or less in a number of series, but is higher in others.[18] Finally, the operative mortality rate is consistently far less than 1%.[18]

Reoperations for persistent or recurrent hyperparathyroidism are more difficult and have a greater potential for hypoparathyroidism, for recurrent nerve injuries, and for failure.[46] Using advanced localization studies, however, up to 90% of these tumors may be found and corrected, in the best of series.[38]

Thus, the results of parathyroid surgery for primary hyperparathyroidism in the 1990s are excellent when done by experienced surgeons. As stated by Malmaeus and coworkers,[52] "These findings strongly advocate special training and interest in parathyroid surgery in order to ensure success."

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ORIGINAL ARTICLES

Cholecystectomy

The Impact of Socioeconomic Change

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The impact of our evolving health care system on a commonly performed surgical procedure, cholecystectomy, was assessed in a county-subsidized and private university hospital setting. Although condition on admission, use of resources, and outcome were unchanged in the private setting between 1980 and 1988, significant differences were noted among the largely uninsured patients at the county facility during this same time interval. There was a significant increase in the acuity of illness among patients undergoing cholecystectomy at the county hospital in 1988 as compared with 1980. These data suggest that alterations in reimbursement strategies and allocation of resources are significantly impacting on patient care, particularly in nonprivate health care facilities.

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DURING THE PAST decade, the American health care delivery system has been challenged by an evolving socioeconomic environment.[1-4] Recent changes in reimbursement strategies and government fiscal priorities, coupled with increasing health care costs, have resulted in limited access to health care for segments of our population and forced the closure of many regional health centers.[5-7] The consequent overcrowding of hospitals, emergency rooms, and clinics has reached crisis proportions in many urban areas. The effects of rising health care costs in combination with limited hospital reimbursement would be expected to be most profound in the inner-city setting, as well as in county- or other government-subsidized hospitals.[8,9] The magnitude of this problem is underscored by the recent development of a Congressional Committee to deal with this issue,[10] and the realization that over 35 million Americans are currently uninsured.[11,12]

As the result of an evolving economic climate, and several local, regional, and national trends, Los Angeles County has experienced a remarkable change in its demographics over the last 10 years. Since 1980, the indigent population of Los Angeles County has increased by approximately 30%, almost one-half million people.[13] During this period, the percentage of county budget appropriations directed toward health services has decreased by 13%, and almost half of the county's trauma centers (10 of 23) have been forced to close.[13] At a time when fiscal support is diminishing, the demand for services is increasing, as reflected by a 32% increase in admissions to Los Angeles County hospitals.[13] This combination of factors has resulted in severe overcrowding of the remaining County health care facilities. Delays of several months before nonemergent patients, such as those with biliary colic, can be treated, are now common in Los Angeles County hospitals. The impact of this increasingly limited access to health care on surgical patient welfare is unknown.

We hypothesized that many of these factors might have a more profound effect on health care delivery in the county as compared with the private setting. The purpose of the present study was, therefore, to identify the trends in the demographics, clinical presentation, and management of patients undergoing a common operation during the past decade at both a county and a private university tertiary care hospital. Traditionally, management of symptomatic gallstone disease has been associated with elective *versus* emergent hospitalization in most patients. The nature of this clinical practice suggested to us that this operation therefore might be susceptible to influence

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by the changing patterns in medical economics. Cholecystectomy therefore was selected as a model for study.

Materials and Methods

Study Design

A retrospective analysis was performed of all patients seen at the Olive View Medical Center (county) and the UCLA Medical Center (private) in the calendar years of 1980 and 1988, who underwent cholecystectomy for calculous disease of the gallbladder. Olive View Medical Center is a large facility, maintained by Los Angeles County, which services primarily indigent patients residing in the San Fernando Valley. The UCLA Medical Center is a university facility that provides predominantly tertiary care. Patients with carcinoma of the gallbladder, pancreas, duodenum, bile duct, and ampulla of Vater were excluded from this analysis, as were patients who underwent incidental cholecystectomy at the time of laparotomy being performed for other reasons. In 1980, 92 patients underwent cholecystectomy at the county facility and 78 at the private hospital, for a total of 170 patients. In 1988, 149 patients underwent cholecystectomy for gallstone disease at the Olive View County Hospital and 61 underwent surgical removal of the gallbladder at UCLA, for a total of 210 patients.

Data were analyzed with respect to demographic factors, admission diagnosis, clinical presentation, acuity, hospital stay, and morbidity and mortality rates. Statistical analyses were performed using Fisher's exact test, and differences were considered significant at the 5% probability level. Results are expressed as mean ± standard deviation.

Results

Patient Population

Demographic factors for patients undergoing cholecystectomy at the county and private hospitals in the years 1980 and 1988 are summarized in Table 1. There were a total of 380 patients available for review at these institutions. Although there was a 62% increase in the number of patients treated at the County hospital in 1988 as compared with 1980, the private university hospital experienced a 17% decrease during this same time interval. The average age of patients undergoing cholecystectomy remained stable during the study period, although it was significantly higher ($p < 0.05$) at the private (49 ± 18 years) as compared with the county hospital (40 ± 16 years). As one would anticipate, most patients in the study were women. Both institutions, however, exhibited a significant increase ($p < 0.05$) in the percentage of men undergoing cholecystectomy in 1988 as compared with 1980. Moreover, the percentage of men seen at the private hospital was significantly higher ($p < 0.001$) during both 1980 and 1988 as compared with the county hospital. Consistent with the patient demographics at the two institutions, most patients at the county hospital in both 1980 and 1988 were Hispanic.

TABLE 1. *Demographic Features*

	County		Private	
	1980	1988	1980	1988
No. of patients	92	149	78	61
Age (yr)	40 ± 16	41 ± 17	49 ± 18[*]	48 ± 17
Sex (% M)	9	19[*][†]	31[‡]	51[§]
Race				
% White	18	19	46[‡]	69[‖]
% Hispanic	77[‖]	72[†]	40	16[‖]
% other	5	8	14	15
Comorbidity (%)	40	39	68	72[‖]

[*] $p < 0.05$ *vs.* county 1980.
[†] $p < 0.001$ *vs.* private 1988.
[‡] $p < 0.001$ *vs.* county 1980.
[§] $p < 0.001$ *vs.* county 1988.
[‖] $p < 0.01$ *vs.* private 1980.

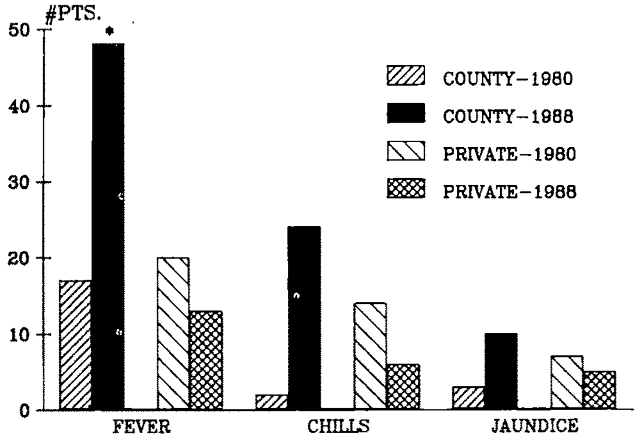

FIG. 1. Incidence of fever, chills, and jaundice among patients undergoing cholecystectomy at private and county hospitals during 1980 and 1988. *$p = 0.03$ *versus* county 1980.

Clinical Presentation

In all four study groups, the most common presenting symptom was right upper quadrant pain. Although 96% of patients presenting at the county hospital in 1980 had right upper quadrant pain, only 81% at the private hospital in 1980 had this as their primary complaint ($p < 0.005$). This difference remained significant in 1988, with only 77% of patients at the private hospital having right upper quadrant pain ($p < 0.01$). Figure 1 represents a comparison of the incidence of fever, chills, and jaundice on admission among County and Private patients during the 2 study years. Although there were no appreciable differences in the incidence of fever, chills, or jaundice in 1980 *versus* 1988 among the private hospital patients, there

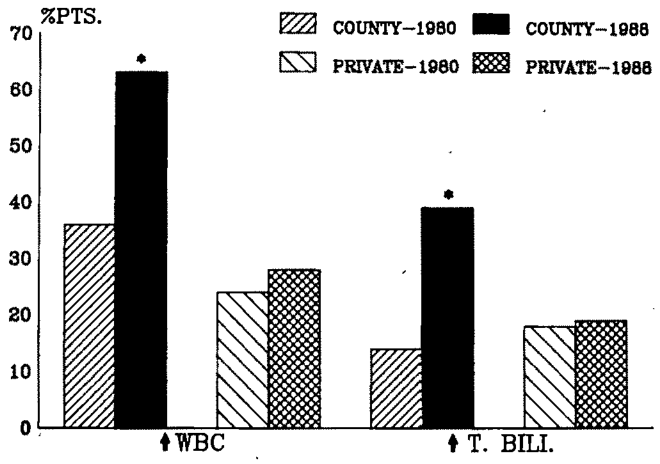

FIG. 2. Comparison of the incidence of leukocytosis and hyperbilirubinemia at the time of admission for cholecystectomy among private and county patients during 1980 and 1988. *$p < 0.005$ *versus* county 1980. Leukocytosis = WBC > 10.0 mg/dL; hyperbilirubinemia = total bilirubin > 1.2 mg/dL.

were marked differences in these indices at the county hospital. Although jaundice was observed in only 4% of patients in 1980 at the county hospital, approximately 10% were noted to be jaundiced in 1988. Similarly, although chills were noted in less than 5% of the patients in 1980, 25% had such complaints in 1988. The most marked difference was in fever, which was present in only 18% of patients at the county hospital in 1980 but in 56% ($p = 0.03$) of the 149 patients who underwent cholecystectomy in 1988 at this facility. Figure 2 summarizes the percentage of county and private patients during 1980 and 1988 who had leukocytosis or hyperbilirubinemia at the time of admission for cholecystectomy. There were no significant differences among the private patients in terms of leukocytosis or hyperbilirubinemia when 1988 figures were compared with those for 1980. In contrast, among patients treated at the county hospital, there were significant increases ($p < 0.005$) in both the incidence of an elevated while blood cell count (63% in 1988 *versus* 36% in 1980) and in hyperbilirubinemia (39% in 1988 *versus* 14% in 1980).

Admission Diagnosis and Level of Acuity

Diagnosis as recorded at the time of admission is summarized for all 380 patients in Figures 3 and 4. Most patients at both the county and private hospitals presented in 1980 with biliary colic as the primary diagnosis. There were no significant differences in the admission diagnoses between the two hospitals for 1980. Although the pattern of admission diagnoses remained remarkably stable at the private hospital during the period of study, there were significant differences noted at the county hospital between 1980 and 1988. Specifically, there was an increase in the percentage of patients presenting with cholangitis, and most notably a significant increase in the fraction of patients presenting with acute cholecystitis ($p < 0.01$ *versus* county—1980), with a concomitant decrease in the incidence of patients operated on for biliary colic.

Based on the nature of the admission, study patients were categorized as being admitted either electively or on an urgent basis (Fig. 5). There were no significant differences noted between the two time periods at the private hospital, with 67% of patients being admitted electively in 1980 and 59% in 1988. In contrast, the percentage of patients presenting urgently at the county hospital increased from 20% in 1980 to 50% in 1988 ($p < 0.001$).

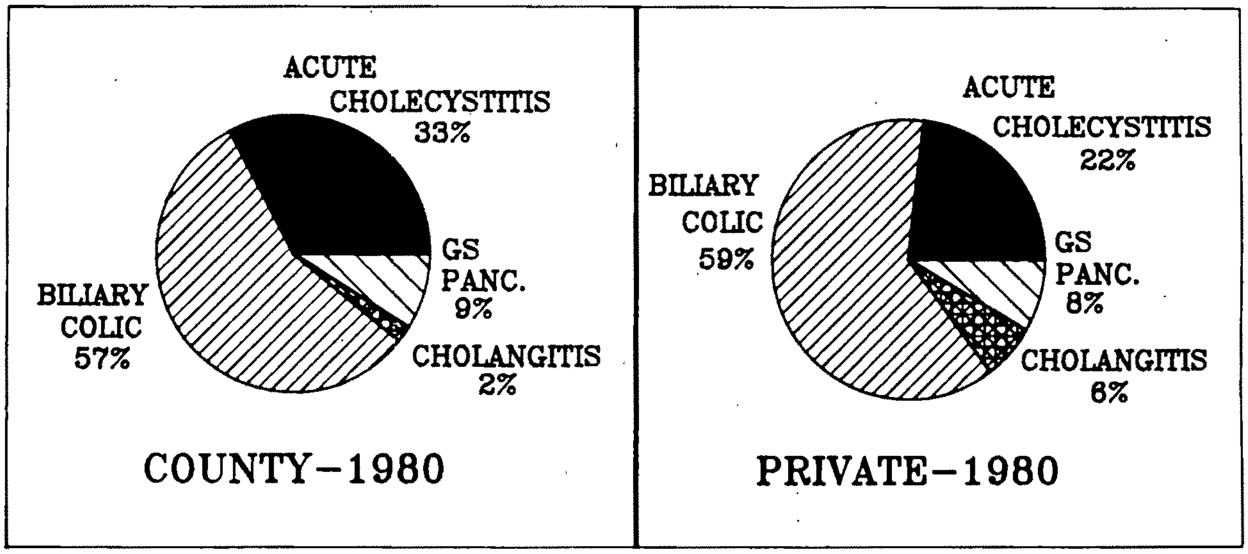

FIG. 3. Comparison of the admission diagnoses for private and county patients undergoing cholecystectomy during 1980.

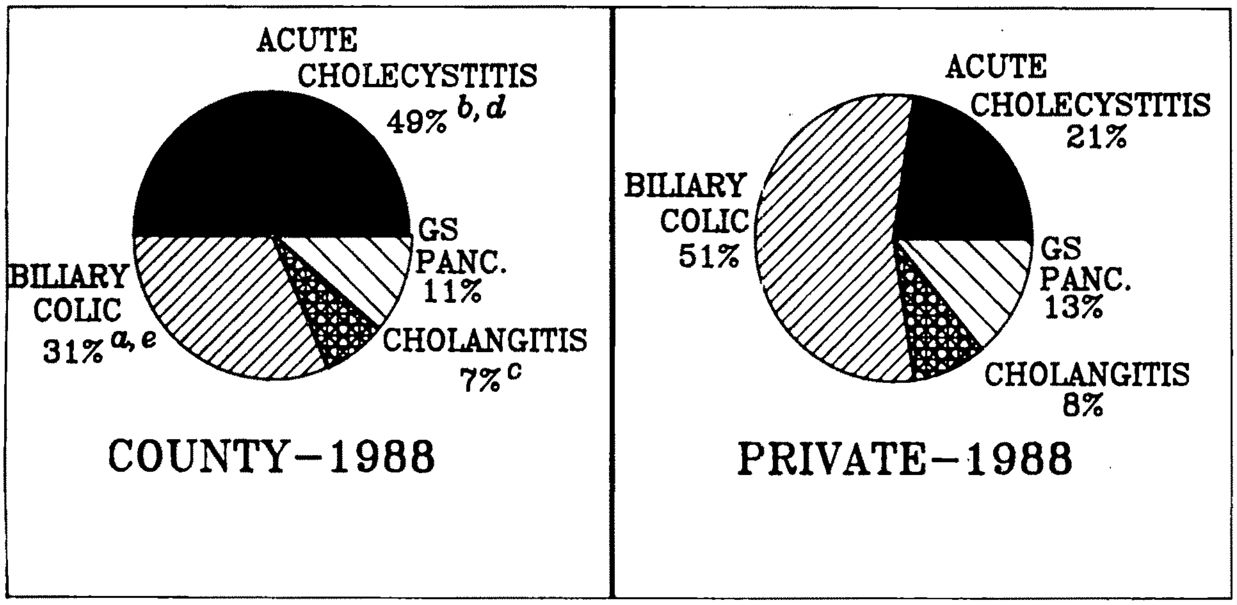

FIG. 4. Comparison of the admission diagnoses for private and county patients undergoing cholecystectomy during 1988. a, $p < 0.01$, b, $p < 0.005$ *versus* private 1988. c, $p < 0.07$, d, $p < 0.01$, e, $p < 0.001$ *versus* county 1980.

Same Day Admissions

Table 2 represents a comparison of demographic features, hospital stay, and outcome for patients admitted on the day of surgery *versus* those admitted at least 1 day before operation. Same day admission (SDA) is a concept that was not employed in 1980, and therefore, the data provided are for 1988 at both county and private hospitals. Not surprisingly, a significantly greater number ($p < 0.005$) of patients were managed by SDA at the private hospital as compared with the county facility. This was true despite the fact that there was a significantly higher percentage of patients at the private hospital who were over the age of 60 ($p < 0.05$) and with a higher incidence of co-morbidity ($p < 0.01$) as compared with the county facility. These factors likely contributed to the higher incidence of postoperative morbidity among private *versus* county patients in the study. Same day admission, per se, did not, however, have any significant impact on morbidity rate at either institution. In fact, postoperative stay for SDA patients was shorter than for non-SDA patients at both institutions.

TABLE 2. *Same Day Admissions*

	County 1988		Private 1988	
	(+)SDA	(−)SDA	(+)SDA	(−)SDA
No. of patients	39 (26%)	110 (74%)	28 (46%)*	33 (54%)
Patient population				
Mean age	42 ± 14	40 ± 17	43 ± 16	52 ± 17
% >60 yr old	10%	18%	25%†	36%
% With comorbidity	38%	30%	71%‡	64%§
Postoperative days				
Mean	5 ± 2	7 ± 4	5 ± 1	8 ± 4
% With ≤5	72%‖	56%¶	68%¶	36%
Morbidity	15%	15%	43%†	52%§

* $p < 0.005$ *vs.* county 1988 (+)SDA.
† $p < 0.05$ *vs.* county 1988 (+)SDA.
‡ $p < 0.01$ *vs.* county 1988 (+)SDA.
§ $p < 0.001$ *vs.* county 1988 (−)SDA.
‖ $p = 0.06$ *vs.* county 1988 (−)SDA.
¶ $p < 0.05$ *vs.* private 1988 (−)SDA.
SDA, same day admission.

Patient Outcome

Overall outcome is summarized for both 1980 and 1988 at the county and private hospitals in Table 3. The overall hospital mortality was 0.2% among the 380 patients who underwent cholecystectomy in this study. The one death occurred in an elderly, immunocompromised patient who underwent emergent cholecystectomy at the private hospital in 1988. The nature of the different patient populations treated at these two institutions is underscored by

TABLE 3. *Patient Outcome*

	County		Private	
	1980	1988	1980	1988
Mortality rate	0	0	0	1 (1.6%)
Morbidity rate	11%	14%	31%*	48%†‡
Hospital days	8 ± 4	10 ± 5	11 ± 6	8 ± 4
Preoperative days	2 ± 1	4 ± 1	3 ± 1	1 ± 1

* $p < 0.005$ *vs.* county 1980.
† $p < 0.001$ *vs.* county 1988.
‡ $p < 0.05$ *vs.* private 1980.

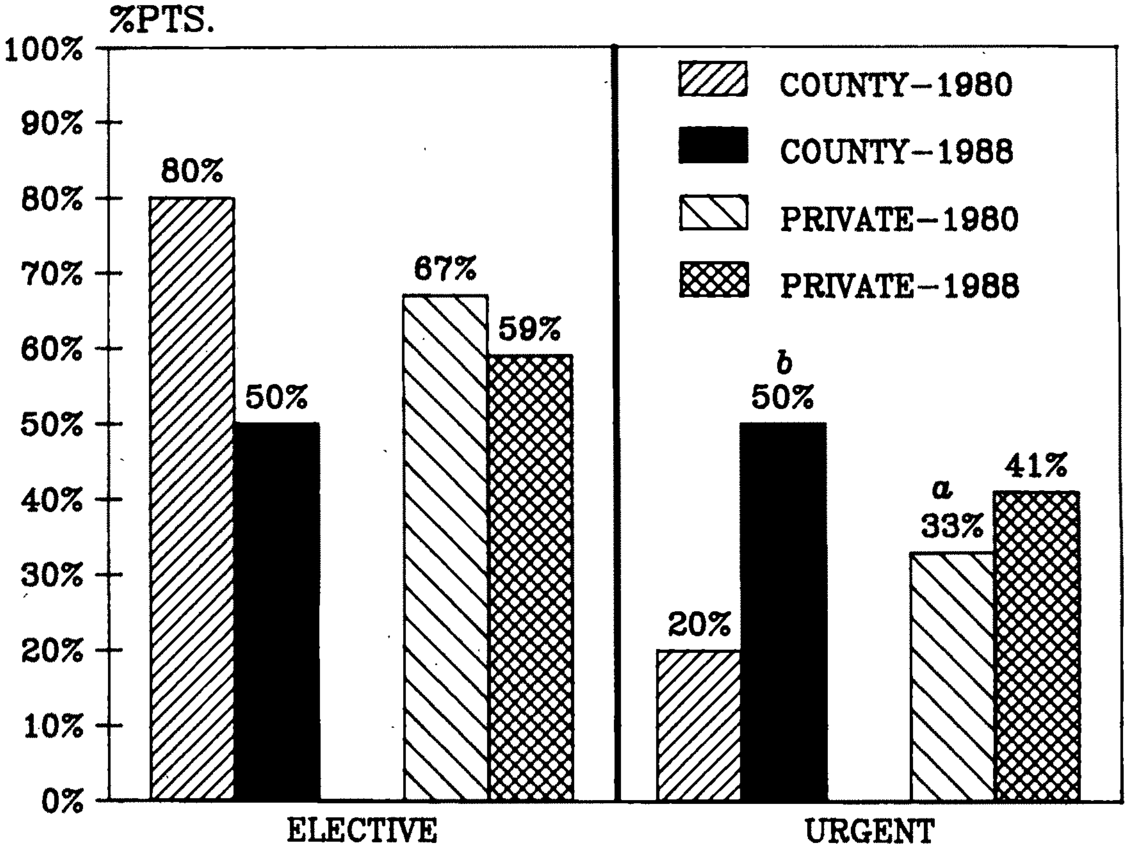

FIG. 5. Comparison of the distribution of elective *versus* urgent admissions among private and county patients undergoing cholecystectomy during 1980 and 1988. Characterizations were based on the degree of illness of the patient at the time of admission. a, $p < 0.05$. b, $p < 0.001$ *versus* county 1980.

the significantly higher incidence of hospital-associated complications noted at the private facility as compared with the county institution during both 1980 and 1988.

Economic pressures have clearly influenced length of stay at the private hospital, resulting in a shortening of the average hospital stay by 3 days during the period of study (Table 3). In contrast, hospital stays at the county hospital actually tended to be longer in 1988 than in 1980 (10 ± 5 days for 1988, *versus* 8 ± 4 days for 1980). Further analysis indicates that this lengthening of hospital stay among county patients occurred during the preoperative period.

Discussion

As one manifestation of the dynamic era in which we practice medicine, physicians throughout the United States are being asked to re-evaluate traditional approaches to patient care.[14,15] The factors responsible for this evolution and rethinking of traditional practices include an explosion in technology with expansion of therapeutic options, patient education, and participation in health care, and perhaps most importantly, socioeconomic influences. The need for hospitalization, length of stay in the hospital, and the total cost associated with specific treatment modalities all have been the target of recent scrutiny.[16–19] Limited resources, rising health care costs, and alterations in hospital reimbursement have combined to affect patient referrals and admission practices. Because of the dependence on government subsidy, the impact of these changes on the business of medicine has presumably had its most profound impact on county- and state-subsidized hospitals. These factors, when coupled with an increasing number of uninsured patients, have led to closure of many facilities,[5–7] ultimately resulting in severe overcrowding of remaining county health care centers.

The current study was undertaken to assess the impact of these socioeconomic changes on the management of a common disorder, gallstone disease. Data from the present study indicate that the patient population presenting for cholecystectomy in the private university setting has remained relatively stable during the last 8 years. In contrast, there has been a significant increase in the acuity of illness among patients undergoing cholecystectomy in the county setting during this same time interval, as reflected by several indices reported in the present study, including the percentage of county patients admitted in 1988 with fever, chills, jaundice, leukocytosis, and hyperbilirubinemia, as compared with 1980. Moreover, patients with admitting diagnoses of cholangitis and acute cholecystitis constituted a much higher proportion of those undergoing cholecystectomies in 1988 than in 1980 at the county hospital. Finally, there was a significant increase in the proportion of county patients admitted on an urgent or emergent basis (50%) in 1988 as compared with 1980 (20%). These data suggest that indigent patients with symptomatic gallstone disease are being treated later in the course of their disease than are insured patients. This disturbing trend seen at the county hospital may reflect lack of health maintenance programs and overburdening of the county medical system with consequent delays and limitations in health care accessibility for the county patient population. The conclusion that the inability to receive medical care is a cause of the increasing percentage of patients with acute cholecystitis is supported by the recent observation that approximately 15% of patients currently undergoing urgent or emergent cholecystectomy were actually on the waiting list for elective cholecystectomy when they experienced an acute exacerbation requiring urgent attention.

The concepts that the quality of care provided to patients, and ultimately patient outcome, are linked to insurance status are not new. In 1977, Egbert and Rothman[20] reported that race and economic status were determinants of whether or not trainees performed patients' surgery. Other more recent studies have confirmed that major differences exist between uninsured and privately insured patients regarding condition on admission, use of resources, length of hospitalization, and outcome.[21-23] Hadley and co-workers[24] investigated the association between insurance status, resource use, and outcome. Their analysis of 592,598 patients hospitalized across the country in 1987 indicated that the uninsured patient was less likely to undergo a high-discretion procedure (such as endoscopy, computed tomography scan, angiography, etc.) and had a significantly greater risk of in-hospital death. Our data support these general observations, and moreover, suggest that the gap between uninsured and privately insured hospital patient is actually widening.

Gallstone disease and its associated complications continue to be major national health problems, with the incidence in the United States being reported to be 10%. In 1882, Carl Langenbuch performed the first successful cholecystectomy. Since that time, surgical removal of the gallbladder has been the only effective treatment for gallstone disease. Over the last several years, laparoscopic cholecystectomy has been introduced and has quickly become the preferred treatment for gallstone disease in many parts of the country.[25,26] The present analysis, however, was completed before the introduction of laparoscopic cholecystectomy, and presumably was not at all influenced by this new modality. Moreover, it remains to be seen to what extent the practice of laparoscopic cholecystectomy will be extended to the indigent population. In recent years, the management of gallstone disease has been affected by a number of other factors, including the controversy over how best to manage a patient with asymptomatic gallstones,[27,28] the technological explosion that we have witnessed in both the medical dissolution of stones[29,30] and biliary lithotripsy,[31,32] as well as socioeconomic influences. These findings may explain two recent reports from single institutions that suggest an increase in the acuity of presentation during the last 10 years for patients with gallstone disease.[33,34] The observation noted in the current study that patients treated at county hospitals for gallstone disease are presenting with more acute and severe disease is particularly concerning in light of recent reports that indicate an increase in hospital-based charges associated with management of acute versus chronic cholecystitis.[19,35]

Almost half of all patients undergoing cholecystectomy at the private facility in 1988 were SDAs. Postoperative complication rates were similar among SDA and non-SDA patients in both institutions. These data suggest that the advent of SDAs has not adversely affected outcome. This information supports the findings from other studies that have suggested that cholecystectomy can be performed safely in a cost-effective manner with a considerably shortened length of hospitalization.[16-18]

Although the length of stay at the private hospital shortened over the 8 years of the study, hospital stay among county patients tended to be longer in 1988 as compared with 1980. Prolongation occurred exclusively in the preoperative period, because patients treated in 1988 may have been "sicker" at the time of admission and, therefore, required additional time for preoperative stabilization. Evidence to support the hypothesis that patients admitted to the county hospital in 1988 were "sicker" as compared with the earlier time period has already been presented. Whether, in fact, the increased time in the preoperative period was required for stabilization or for operating room availability cannot be determined from the present study. A likely explanation, however, is that limited resources in the operating room have led to overcrowding with acutely ill and trauma victims and the development of a priority system for case selection based on degree of urgency. Over the last several years, severe demands on operating room resources has led to the implementation of just such a system at the Olive View Medical Center. The hospital is continually filled to capacity, and there is a 4- to 6-week wait for new evaluations in the outpatient clinic. A waiting list has been generated for elective and "urgent" (rule out cancer) surgical cases, which as of June 30, 1991, totaled 515 patients for General Surgery, 112 of which were considered "urgent." Currently, patients with uncomplicated, symptomatic cholelithiasis are waiting a total of 3 to 4 months for elective surgery.

Data are not available for cost analysis of patients treated at either the university or the county hospitals. The computation of direct and indirect costs associated with the provision of health care is obviously very complex and is dependent on a number of factors that are beyond the scope of this study. Therefore, one cannot accurately judge whether the strategy of resource restriction actually increased the cost of care for patients treated at the County facility. Munoz and co-workers,[19] however, have previously reported data demonstrating that the cost of treating patients with acute cholecystitis is at least twice that for patients undergoing an elective procedure. Although data were not available for the 380 patients in the present study regarding cost, Munoz and co-workers[19] have reported that the cost of emergent cholecystectomy is 240% of the cost of an elective procedure.

Our data indicate that unfunded or underfunded patients enter the health care system later and with more advanced disease than even a decade ago. Despite these changes, there were no differences noted between groups in terms of outcome. Currently,, cholecystectomy as it is practiced in the United States is safe and is associated with a minimal mortality rate regardless of age or severity of illness. In a series of 18,562 patients undergoing cholecystectomy in California and Maryland during 1988, the overall mortality rate was 0.23%, with a range from 0.03% for patients under the age of 65 years to 0.87% for elderly patients.[35] It may be difficult, if not impossible, therefore, to demonstrate that timing of intervention or acuity of illness effects outcome. Data clearly indicate, however, that acuity of illness has a significant impact on length of stay, use of resources, and hospital-based costs for patients being treated for gallstone disease.[19,35] The broader issue, however, remains unclear: has the reduction in services and associated limitations of access to health care that is occurring nationwide affected patient welfare and outcome? Although this question has not been answered by the current study, we believe that our data raise legitimate concerns that in government-subsidized facilities, the care of the surgical patients is and will be adversely influenced by ongoing socioeconomic changes.

As our health care delivery system responds to the stresses of an evolving economic environment, it is essential that physicians monitor the impact of these socioeconomic changes on the quality of patient care. With its relatively high incidence in the patient population, characteristic presentation, and limited therapeutic options, gallstone disease provides an ideal model for the evaluation and study of the effects of health care delivery practices on patient outcome. The reality is that physicians should and must take responsibility for developing cost-effective health care allocation, and optimal patient management.[36,37] While we are attempting to be cost effective, however, it is imperative that we monitor the effects of these changes on patient outcome and general welfare, as well as the ultimate impact on the health care delivery system at large. This information should be considered in the ongoing evaluation and restructuring of our health care delivery system.

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Inapparent Carcinoma of the Gallbladder

An Appraisal of a Radical Second Operation After Simple Cholecystectomy

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This study was designed to investigate issues concerning "inapparent carcinoma" of the gallbladder and the effectiveness of a radical second operation in the treatment of inapparent carcinoma. Ninety-eight patients with inapparent carcinoma were analyzed according to the "pT" category of TNM (tumor, nodes, and metastases) classification. Eighty patients underwent cholecystectomy alone, and 14 patients had a subsequent radical operation. After cholecystectomy alone it was found that (1) Patients with pT1 cancer had a 5-year survival rate (5ysr) of 100%; (2) In patients with pT2, 5ysr was 40%; and (3) Patients with pT3 showed 5ysr of 0%. Results of a radical second operation showed that (1) Patients with pT2 cancer showed a 5ysr of 90%, significantly better ($p < 0.05$) than pT2 treated with cholecystectomy alone; (2) There was a prolongation of survival in patients with pT3 or pT4. It was concluded that a radical second operation should be carried out for pT2 or more advanced inapparent carcinoma, whereas follow-up without a second operation is recommended for pT1 cancer without positive margin.

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CARCINOMA OF THE GALLBLADDER has been considered to be a highly lethal disease.[1-3] Although a few long-term survivors have been reported, most of them were patients with gallbladder carcinoma first diagnosed on microscopic examination after simple cholecystectomy, that is, "inapparent carcinoma" of the gallbladder.[4-7] It has been clear, however, that the prognosis in inapparent carcinoma was not uniformly good, and many of the reported patients died of recurrence.[5-7]

Reoperation after first cholecystectomy for inapparent carcinoma has been recommended by some investigators,[6-10] but there has been no study thus far that clearly demonstrates whether reoperation with a radical procedure could improve the prognosis for inapparent carcinoma of the gallbladder. The present study was designed to address issues concerning inapparent carcinoma: (1) the prognosis for inapparent carcinoma treated with cholecystectomy alone, (2) the types of inapparent carcinoma that can be cured with cholecystectomy alone, and (3) does the radical second operation improve the survival of patients with inapparent carcinoma?

Patients and Methods

Two hundred forty-one patients with gallbladder carcinoma underwent surgical resection in Niigata university hospital and its affiliated institutions from 1981 to 1989. A summary of these cases is provided in Table 1. In the present study, "inapparent carcinoma" of the gallbladder was defined as a carcinoma unrecognized before and at the time of operation, but diagnosed later on microscopic examination of the specimen. Therefore, 98 cases (41%) of "inapparent carcinoma" were included in this study. Clinical records and follow-up data could be obtained for all of them.

Histologic examination of these specimens was done in the first department of pathology of our institute. In 86 cases 5-mm stepwise tissue sections of the whole gallbladder were embedded in paraffin and cut into 4-μm slices. The depth of cancer invasion was carefully determined in these sections. In the remaining 12 cases, depth of invasion was judged using three to four representative sections containing evidence of cancer.

We used the TNM (tumor, nodes, metastases) system[11,12] to describe the extent of the cancer. Depth of cancer invasion corresponds with the "T" category in this system. However, "N" and "M" categories of inapparent carcinoma could not be assessed in almost all cases, because the cancer had not yet been noticed at the time of the first operation. It also follows that the "Stage" could

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TABLE 1. *Patients Who Underwent Resection for Gallbladder Carcinoma at the Department of Surgery, Niigata University, 1981–1989*

Time of Diagnosis	No. of Cases
Before operation	102
At the time of operation	41
After operation (inapparent carcinoma)	98
Total	241

not be determined in many of the cases. The authors therefore adopted the pathologic T category (pT) alone to describe the extent of inapparent cancer of the gallbladder. The pT system is defined in TNM system as follows[11,12]: pT1: tumor invades mucosa or muscle layer; pT2: tumor invades perimuscular connective tissue; no extension beyond serosa or into liver; pT3: tumor invades beyond serosa or into one adjacent organ, or both (extension 2 cm or less into liver); and pT4: tumor extends more than 2 cm into liver, or into two or more adjacent organs.

The survival curves were calculated using the Kaplan-Meier method. Differences in survival curves were measured using the generalized Wilcoxon test.

Results

Ninety-eight cases of inapparent carcinoma are categorized according to their "T" classification and type of operation performed in Table 2. There were 24 men and 74 women. The age of these patients ranged from 37 to 87 years, with a mean of 68.5 years.

Eighty patients had cholecystectomy alone, and 14 patients had a radical second operation after pathologic confirmation of the specimen removed at the time of cholecystectomy. The remaining four patients also underwent reoperation after histologic confirmation of cancer. They had no radical procedure, however, but sampling of pericholedochal lymph nodes alone at the time of reoperation, with regard to no macroscopic evidence of residual cancer.

TABLE 2. *Distribution of pT Category of 98 Patients With Inapparent Carcinoma According to Operations Performed*

	Operations Performed			
pT	Cholecystectomy Alone	Second Radical Operation	Other Operations*	Total
pT1	39	1	—	40
pT2	35	10	3	48
pT3	6	2	1	9
pT4	—	1	—	1
Total	80	14	4	98

* Refer to the text for the details of the operations.

Cholecystectomy Alone

Follow-up data of the 80 inapparent cancer patients who underwent cholecystectomy alone is presented according to their "pT" classification in Figure 1. There were no pT4 patients.

The 39 patients with pT1 cancer had a 5-year survival rate (5ysr) of 100%. There were 35 cases of cancer rated as pT1a and 4 cases of pT1b. Only two patients with pT1a cancer died, one at 19 months and the other 66 months after surgery; the former, who had mucosal cancer with a free surgical margin, died of an unrelated cause, and the latter, who had a mucosal cancer with a positive margin at the cut stump of the cystic duct, died of recurrence of the tumor at the hilus of the liver. There was no recurrence among the pT1b patients; the longest period of survival so far is 98 months. In the 35 patients with pT2 cancer, 5ysr was 40%, and 17 patients died of recurrent disease within 55 months postoperatively. All of the six patients in the pT3 group died of recurrence within 27 months after cholecystectomy.

There were significant differences between pT1 and pT2 groups ($p < 0.001$) and between pT2 and pT3 groups ($p < 0.01$), respectively (Fig. 1).

There were 36 cases in which the cholecystectomized specimen included a cystic lymph node. In six cases, there was evidence of metastasis to the lymph node; five of these patients died within 45 months from recurrence, and only one has survived 36 months so far. The remaining 30 patients who had no metastasis to the node showed a significantly better ($p < 0.001$) prognosis, and a 5ysr of 84%.

Radical Second Operation

A radical second operation (after cholecystectomy) was carried out in 14 of the 98 cases with inapparent carcinoma. Table 3 presents a brief summary of the 14 patients. The radical second operation was performed for pT2, 3, or 4 inapparent cancer or a positive surgical margin.

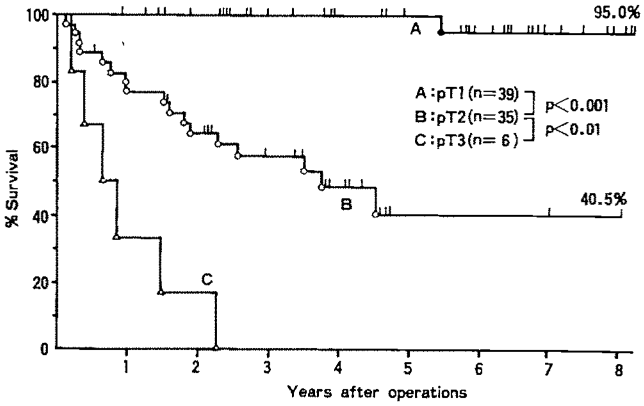

FIG. 1. Survival curves by pT category in 80 patients with inapparent carcinoma treated by cholecystectomy alone.

TABLE 3. *Patients With Inapparent Carcinoma Treated by Second Radical Operation*

Patient	Age (yr)	Sex	pT	pN	M	Stage	Cancer Tissue in Reresected Specimen	Residual Tumor (R) at 2nd Resection	Survival	Status	Cause of Death
1	72	M	1a	0	0	I	Not detected	R0	56 mo	Alive	—
2	37	F	2	0	0	II	Not detected	R0	18 mo	Alive	—
3	72	F	2	0	0	II	Detected: C	R0	22 mo	Alive	—
4	62	M	2	0	0	II	Not detected	R0	63 mo	Alive	—
5	58	M	2	0	0	II	Not detected	R0	65 mo	Alive	—
6	62	F	2	0	0	II	Not detected	R0	67 mo	Alive	—
7	69	F	2	0	0	II	Not detected	R0	86 mo	Alive	—
8	45	F	2	0	0	II	Not detected	R0	91 mo	Alive	—
9	76	F	2	1a	0	III	Detected: N, B	R1	44 mo	Dead	Renal cell cancer
10	72	F	2	1a	0	III	Detected: N, C	R0	105 mo	Alive	—
11	66	F	2	1b	0	III	Detected: N	R0	13 mo	Dead	Recurrence
12	66	F	3	0	0	III	Detected: C, L	R2	14 days	Dead	Complications after operation
13	74	M	3	1a	0	III	Detected: B, C	R1	59 mo	Dead	Recurrence
14	70	F	4	1b	0	IV	Detected: N, B, C, L	R2	17 mo	Dead	Recurrence

C, invasion of connective tissue around the gallbladder; N, metastasis to regional lymph nodes; B, invasion of bile duct; L, invasion of liver parenchyma.

The "standard" radical operation in our department since 1982 adopted as a first operation for preoperatively diagnosed gallbladder carcinoma is illustrated in Figure 2. The operation is composed of a cholecystectomy, wedge resection of the gallbladder bed (including about 2 cm thickness of liver parenchyma), resection of the supraduodenal segment of the extrahepatic bile duct, and an *en bloc* and thorough dissection of the regional lymph nodes (No. 1a and 1b nodes). As a surgical approach to management of inapparent cancer, the "standard" radical second operation was therefore composed of bile duct resection, wedge resection of the gallbladder bed, and an *en bloc* dissection of regional lymph nodes (No. 1a and 1b nodes). All patients except patients 1 and 10 listed in Table 3 underwent the "standard" radical second operation. In patient 1, the second resection was indicated because of a positive margin at the cystic duct, and a wedge resection of gallbladder bed was deferred in consideration of the depth of cancer invasion (pT1a). Bile duct resection was not performed in patient 10 because, in 1981, the standard for the radical operation had not been established.

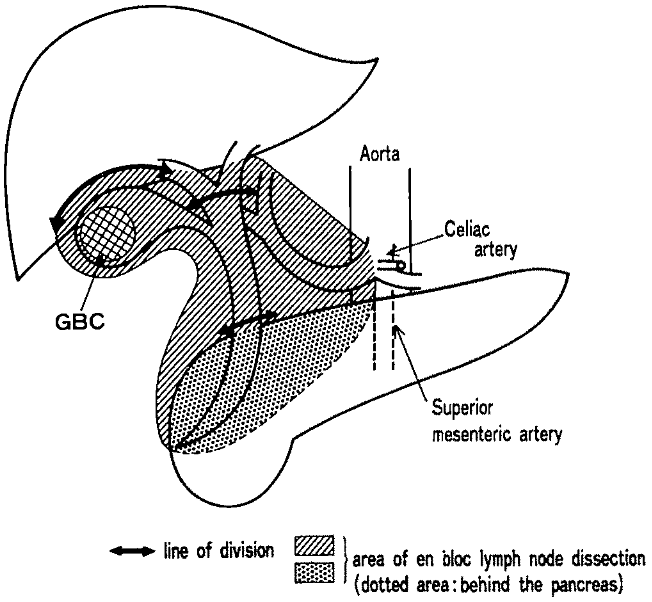
Aorta
Celiac artery
GBC
Superior mesenteric artery
line of division
area of en bloc lymph node dissection
(dotted area: behind the pancreas)

FIG. 2. Schematic representation of the extent of surgical resection in patients with gallbladder cancer.

As shown in Table 3, cancer tissue could be histologically proven in the tissue resected in the radical second operation in seven patients. In four of the seven patients, complete removal of the cancerous tissue could not be achieved by the second operation, and microscopic or macroscopic residual tumor (R1, R2) was identified. All of the 4 patients died by 59 months after the second resection; 2 of them died of recurrence of gallbladder cancer, 1 died of renal cell carcinoma, and another died of a postoperative complication (bleeding).

Thus far, one case of pT1 cancer survives 56 months after the second operation, and eight of the ten cases of pT2 continue to survive, with the longest time of survival being 105 months. All three cases with pT3 and pT4 have died.

To evaluate the efficacy of a radical second operation, the survival of patients with pT2 inapparent cancer treated by cholecystectomy alone were compared with those treated by the radical second procedure (Fig. 3). Survival of the group receiving the radical second operation was significantly better than cholecystectomy alone ($p < 0.05$).

DISCUSSION

In Japan, many gastroenterologists have a great interest in the early diagnosis of gallbladder carcinoma (GBC) be-

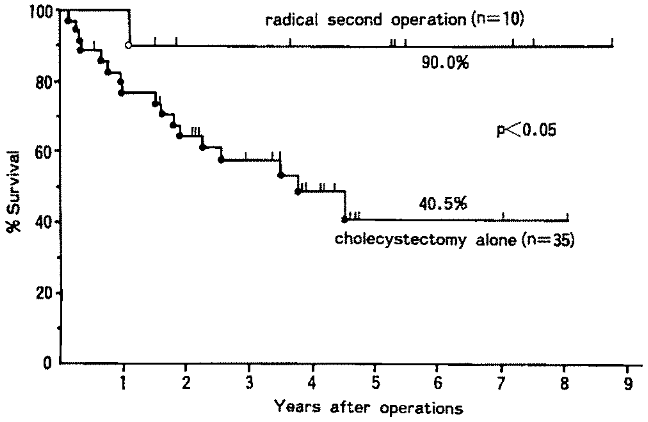

FIG. 3. Comparison of survival curves of patients with pT2 inapparent gallbladder carcinoma undergoing cholecystectomy alone and cholecystectomy combined with a radical second surgical resection.

cause of the high mortality rate of GBC in the Japanese population.[13] In spite of recent developments of diagnostic imaging, it is still difficult to diagnose GBC preoperatively. The present study showed that the preoperative diagnostic rate was rather low, 42% (102 of 241), and inapparent carcinoma was present in 41% of our patients.

It has been widely accepted that some cases of inapparent cancer have a good chance to be cured, and clinically overt cancer is often far advanced and beyond the scope of resection.[1-3] It is likely that inapparent cancer tends to be in the early stages.[10] Many of the cases of inapparent cancer observed in this study belonged to pT1 or pT2 (Table 2).

There are two issues concerning the treatment of inapparent carcinoma of the gallbladder. The first issue is that there are many patients with inapparent carcinoma who cannot currently be diagnosed preoperatively, and the second issue is that inapparent carcinoma is a good candidate for radical surgery because of the demonstrated predominance of earlier stages. A radical second operation for inapparent carcinoma, therefore, appears to be an effective way to improve the poor prognosis of GBC.

Most long-term survivors of GBC have been considered to be patients with inapparent cancer treated with cholecystectomy alone.[4-7] Nevin et al.[14] proposed a staging system and reported that the prognosis of GBC depended mainly on the depth of cancer invasion. Carcinoma confined to the mucosa or the tunica muscularis showed an excellent prognosis after being treated by cholecystectomy alone, but once the cancer involved all three layers, liver, or any other organ, the results of surgery were poor. Some investigators also have reported good results with surgery for patients with carcinoma confined to the mucosa or the tunica muscularis.[9,15]

The present study demonstrated that cholecystectomy alone provided excellent results in patients with pT1 cancer. For this reason, a radical second operation should be avoided in the pT1 inapparent cancer group. However, pT2 and pT3 inapparent cancer had little chance to be cured by cholecystectomy alone and so a radical second operation should be considered if possible.

Glenn and Hays[16] proposed radical surgery for GBC in an excellent paper published in 1954. This radical procedure, commonly called "Glenn's operation," seems to have been widely accepted. This operation has been thought to be an adequate operation for GBC in early stages. The lymph node dissection in this operation is commonly referred to as "skeletonization of the lesser omentum."

In our department, the operation illustrated in Figure 2 has been adopted as the standard operation for "apparent" GBC except in pT1 tumor. This operation differs from Glenn's in that bile duct resection is performed in our operation to clear the lymphatics around bile duct and possible presence of invasion of bile duct, and lymphatic system behind the upper part of the head and neck of the pancreas is removed *en bloc*. We designed the scope of the nodal dissection on the basis of the data from Fahim et al[17] and our own data (unpublished observations) relating to the routes of lymphatic drainage from the gallbladder and patterns of nodal metastasis in GBC.

In the radical second operation, the same degree of nodal dissection as in the operation illustrated in Figure 2 should be performed. Although it was impossible to remove completely cancerous tissue even in the radical second operation in some patients, it was thought that the results justified the surgical intervention (Table 3). Tsunoda et al.[8] reported on three patients with inapparent cancer who underwent a second-look operation. The authors, however, could not definitely comment on the efficacy of the second-look operation due to the small sample size. De Aretxabala et al.[10] aggressively performed a radical second operation including lymph node dissection and hepatic wedge resection for patients with inapparent GBC. They did not report long-term results of the operation, however, and concluded that further follow-up was required to assess the long-term value of this approach. In the present study, we were able to demonstrate that the radical second operation was especially effective against pT2 cancer (Fig. 3). Although the number of pT3 and pT4 cancers treated with the radical second operation was small, it is important to note that one case of pT3 and one case of pT4 survived 59 months and 17 months, respectively, after the operation. In consideration of the extremely poor prognosis (Fig. 1) of pT3 inapparent cancer patients who underwent cholecystectomy alone, the results (Table 3) of the radical second operation in pT3 and pT4 suggest a prolongation of survival time.

Indications for a Radical Second Operation for Inapparent Cancer

Based on the results of this study, indications for a radical second operation for inapparent carcinoma are proposed in Table 4. It was demonstrated that pT1 cancer patients had an excellent survival with cholecystectomy alone. Therefore, if the depth of cancer invasion is judged to be limited to the mucosa or the muscle layer and the surgical margin, on histologic examination, is negative, the patient should be followed without recourse to a radical second operation. Prognosis of pT2 and pT3 cancer treated by cholecystectomy alone was unfavorable and was improved by a radical second operation. Therefore, the radical second operation should be indicated for pT2 or more advanced inapparent GBC. A second resection also should be considered for inapparent cancer with positive margin, regardless of the depth of invasion. When a carcinoma is found in the gallbladder removed for presumed benign disease, the cystic duct node, when found, should be examined histologically. In the case of a positive cystic node, which indicates short-term recurrence, a radical second operation should be considered.

Once a carcinoma was found in a gallbladder removed for benign disease, the depth of cancer invasion, the resection margin, and the state of the cystic node should be precisely determined by detailed pathologic examination. The depth of cancer invasion in the specimen is the most reliable criterion for a radical second operation. Although some authors[5,8,18] have reported some recurrences in patients with carcinoma invading the muscular layer (pT1b), others[14,15] have reported good results in patients with pT1a and pT1b cancers treated with cholecystectomy alone. On the basis of the results of cholecystectomy alone for pT1 cancer in this study, we do not think that a radical second operation is indicated for pT1 cancer with negative margin. The sample size of pT1b cancer, however, is so small and the follow-up period is so short that further investigation is required to conclude the indication of the radical second operation for pT1b inapparent cancer.

On histologic evaluation of the depth of invasion of GBC, it is often difficult to distinguish pseudoinvasion into the Rokitansky-Aschoff sinus (RAS) (*i.e.*, RAS involvement) from true, stromal invasion. Shirai[19] previously reported an attempt at a histologic differentiation of these two. RAS involvement is not a stromal invasion but an intraepithelial spread, that is, carcinoma *in situ.* Gallbladder carcinoma with RAS involvement in the muscle layer and subserosal layer, without stromal invasion, therefore, is judged to be a mucosal cancer (pT1) and is not a candidate for the radical second operation in our department.

TABLE 4. *Indications for Radical Second Operation for Inapparent Carcinoma of the Gallbladder*

pT2 or more advanced carcinoma
Positive surgical margin
Positive cystic duct node (if examined)

One patient who underwent the radical second operation for stage III cancer died of bleeding within a month after operation in the present study. The operative procedure of the radical second operation is difficult because of adhesions caused by the first operation. We think that indications for the radical second operation should be carefully weighed.

The resected gallbladder should be examined intraoperatively in all cases of cholecystectomy for presumed benign disease to detect "inapparent gallbladder cancer" to avoid a second operation. The surgeon should open the gallbladder immediately after removal and observe the mucosa to detect unexpected cancer. Some investigators reported that the predominant macroscopic shape of early-staged carcinoma of the gallbladder was the superficial type.[20,21] Knowledge concerning macroscopic features of gallbladder cancer[20,21] is useful in detecting suspicious lesions. Histologic examination of a frozen section of the lesion is mandatory to prevent overlooking a cancer.

Because the number of patients who underwent the radical second operation is small in this study, further investigation is warranted to clarify the true indications and the advantages of the radical second operation.

Conclusions

It was concluded that a radical second operation should be carried out for pT2 or more advanced inapparent carcinoma of the gallbladder whenever possible. Follow-up without a second resection is the treatment of choice for pT1 cancer with free margins. The radical second operation should contribute to a better salvage rate in this lethal disease.

Acknowledgments

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Stress Ulcers and Organ Failure in Intubated Patients in Surgical Intensive Care Units

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This study compared prophylactic administration of either intragastric misoprostol (200 μg four times a day), a prostaglandin E_1 analog, or bolus intravenous cimetidine (300 mg every 6 hours) in preventing stress lesions and stress bleeding in 127 adult postoperative patients who required mechanical ventilation and also had developed hypotension or sepsis. Both drug treatments were equally effective in preventing the development of diffuse gastritis (>10 gastric hemorrhagic lesions) and in preventing upper gastrointestinal hemorrhage (UGIH). The combined data from both groups showed that for the 44 (35%) patients who died, death was significantly associated with the presence at study entry of renal failure (64% of 25 patients with renal failure died), hepatic failure (57% of 23 patients) or coagulopathy (62% of 29 patients) ($p < 0.02$ for each), and with the number of organ system failures at study entry (48% of 69 patients with multiple organ system failures died, $p < 0.001$). Death was also significantly associated with the presence of adult respiratory distress syndrome (ARDS) at study entry or the development of ARDS (63% of 24 patients with ARDS died, $p < 0.001$), and the development of UGIH (5% of 93 patients with known bleeding outcome died, $p < 0.05$). The number of stress lesions that developed was significantly associated with subsequent UGIH ($p < 0.001$). Additional organ system failure developed during the study in 31% of the 127 patients, as did diffuse gastritis in 20% of 111 patients who had a follow-up endoscopy. These results demonstrate that postoperative patients who require mechanical ventilation and have hypotension or sepsis are at significant risk for the development of stress gastric lesions and multiple organ system failure even when prophylaxis for stress ulcers is provided. Furthermore, the presence of ARDS, renal failure, hepatic failure, coagulopathy, and UGIH are significantly associated with death.

HEMORRHAGE FROM STRESS-INDUCED gastric lesions (stress ulcers) was a significant problem in many critically ill surgical patients in the 1960s who had sepsis and evidence of organ failure.[1] Hemorrhage from stress ulcers has been defined as gut failure in the multiple organ failure syndrome[2] and continues to be associated with high mortality rates when it develops postoperatively.[1,2]

The development of postoperative pneumonia is also associated with high mortality rate.[3] The risk of death is significantly associated with pneumonia that develops during mechanical ventilation when evidence of other organ failure is present.[3] Studies[4,5] have recently suggested that prophylactic administration of agents designed to increase gastric pH to decrease the risk of hemorrhage from stress ulcers may increase the risk of the development of pneumonia in patients requiring mechanical ventilation. Only one of these studies showed a significant association between pneumonia and antacid administration; neither study was blinded. These reports have stimulated a reevaluation of prophylaxis of stress-induced bleeding, however. Currently, there is less consensus on what prophylactic treatment is indicated than at any time since Hastings and colleagues[6] demonstrated that antacids decreased the incidence of microscopic bleeding.

This report presents the results from 127 patients from 25 medical centers who were prospectively identified to be at high risk for the development of upper gastrointestinal hemorrhage (UGIH), using previously published criteria,[7] within 2 weeks of a surgical operation, and who also required mechanical ventilation. Although there have been many reports of various methods of preventing UGIH in intensive care unit (ICU) patient populations, few of these controlled studies have examined exclusively postoperative patients who have organ failure and other risk factors associated with bleeding at entry. Even fewer

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have endoscopically examined gastric mucosa to determine how the development of lesions related to the development of UGIH.

This report examines patients at the brink of the development of multiple system organ failure (MSOF). It also examines how the presence of MSOF influences the development of UGIH and the outcome and development of other complications, including pneumonia, by prospectively recording which other risk factors were present at entry.

Materials and Methods

This was a randomized, double-blind, double-dummy stress ulcer prophylaxis study performed at 25 medical centers in the United States. At each of these institutions, the protocol was approved by the Institutional Review Board. Written informed consent was obtained from the patient or surrogate before study entry. Patients were enrolled between July 1986 and January 1988. Adult men and nonpregnant women in an ICU who had undergone a surgical procedure requiring general anesthesia within 14 days before meeting the other entry criteria were considered eligible. Additionally, patients had to be intubated, require mechanical ventilation support, and experience an episode of either hypotension (systolic pressure < 90 mmHg or require medication to maintain blood pressure) or sepsis (positive blood cultures or clinical evidence of systemic infection) to be considered for enrollment.

Exclusion criteria included psychiatric disorders requiring medication, upper gastrointestinal (UGI) malignancies, inflammatory bowel disease, active peptic ulcer disease, and burns. Also excluded were patients with recent central nervous system damage, head injury requiring neurosurgical intervention, or unstable spinal fractures. Patients who had had UGI surgery proximal to the ampulla of Vater within 30 days and patients not expected to survive at least 14 days also were excluded. Patients receiving nonsteroidal anti-inflammatory agents, anti-ulcer agents, or anti-neoplastic agents as well as those with known allergies to either of the study medications were not eligible.

Once informed consent had been obtained, but before randomization, patients underwent a screening endoscopy. The gastric and duodenal mucosae were graded according to the scoring system presented in Table 1. Patients with a score of 5 or more for either stomach or duodenum were considered ineligible for prophylaxis and were excluded from the study.

TABLE 1. *Endoscopic Grading System for Gastroduodenal Mucosa*

Grade	Description
1	Normal mucosa or hyperemic changes
2	A single hemorrhagic lesion
3	2–5 hemorrhagic lesions
4	6–10 hemorrhagic lesions
5	Large areas of confluent hemorrhagic lesions
6	Erosions with white bases surrounded by erythematous edges
7	Ulcer craters

Patients who met eligibility criteria then were randomized to receive either active misoprostol 200 μg (G.D. Searle & Co., Skokie, IL), a new prostaglandin E_1 analog, mixed in 20 mL of water every 4 hours through their nasogastric (NG) tube and intravenous placebo every 6 hours, or placebo tablet mixed in water through the NG tube, and active intravenous cimetidine 300 mg (Smith Kline Beecham, Philadelphia, PA) every 6 hours. Patients were studied until one of three events occurred: (1) 2 weeks of ICU management were completed, (2) improvement allowing discharge from the ICU, or (3) the development of significant UGIH. Additionally, patients could be removed from the study if the investigator or the patient's personal physician thought it was in their best interest to do so.

Significant UGIH was considered a sign of organ failure and was defined by any one of the following:

1. The occurrence of hematemesis, melena, or hematochezia.
2. The presence of bright red blood in the NG aspirate that did not immediately clear after lavage with 250 mL normal saline.
3. A drop in hemoglobin concentration over two consecutive measurements of at least 2 mg/dL with stools that had positive Hematest (Smith Kline Beckman, Sunnyvale, CA) results that were not attributable to other causes.

The development of UGIH was an endpoint for this study and therefore was not included in any calculations that involved numbers of organ system failures.

Patients meeting the above criteria for bleeding underwent an endoscopic evaluation within 12 hours and were removed from the study if a UGI bleeding source was confirmed. All patients still in the study at 72 hours underwent a follow-up endoscopy to determine whether the condition of the gastric or duodenal mucosa had changed. When possible, patients also underwent an endoscopy on exit from the study. If a patient underwent more than one follow-up endoscopy, the score that represented the most severe damage was used.

Patients were studied for the presence or development of other organ system failures as defined in Table 2. Complications were recorded prospectively using the risk criteria suggested by Zinner et al.[7] Recent publications[4,5] that have emphasized the potential relationship between stress ulcer prophylaxis and pulmonary problems stimulated us to retrospectively review data relevant to this issue as carefully as possible. All the investigators who

TABLE 2. *Definitions of Organ System Failures*

Organ	Definition
Pulmonary*	Mechanical ventilatory support
Renal	Serum creatinine value >3.0 mg/dL
Coagulopathy	Platelet count of <50,000/mm^3 or prothrombin time >30% higher than control level
Hepatic	Bilirubin value >5 mg/dL or transaminase value >3 times the upper limit of normal
Gastrointestinal†	A drop in hemoglobin value of ≥2 mg/dL, hematemesis, melena, hematochezia, or bright red blood via nasogastric tube
Cardiac	Congestive heart failure requiring therapy other than diuretics or digitalis, or myocardial infarction
Adult respiratory distress syndrome‡	Hypoxia that required ventilator support for >72 hr

* Required for study inclusion.

† This was an endpoint for the study and thus was not included in calculations of organ failure.

‡ Ongoing need for ventilatory support (see text) or reintubation for pulmonary problems was considered a new sign of organ failure.

TABLE 3. *Clinical Characteristics of Patient Populations on Admission*

Characteristics	Misoprostol (n = 63)	Cimetidine (n = 64)
Age (mean ± SD)	60.2 ± 15.2	59.9 ± 17.5
Sex (M/F)	39/24	40/24
White/nonwhite	51/12	46/18
Risk factors at entry		
Hypotension	52	53
Sepsis	47	48
Coagulopathy	15	14
Renal failure	13	12
Hepatic failure	11	12
Cardiac failure	9	13
Adult respiratory distress syndrome	6	8
No. of gastric lesions		
None	15	19
1–5 hemorrhagic lesions	24	30
6–10 hemorrhagic lesions	23	13
Unknown	1	2
No. of duodenal lesions		
None	60	61
1–5 hemorrhagic lesions	1	0
Unknown	2	3

submitted data to this study made a distinction between patients requiring short-term postoperative ventilatory support and those who had additional complicating conditions such as pneumonia or adult respiratory distress syndrome (ARDS). Bronchial culture data, however, were not routinely collected and, therefore, diagnostic criteria for pneumonia were inconsistently available. We therefore chose to classify as ARDS cases those patients who developed both of the following features:

1. They were labeled by their investigator as having either pneumonia or ARDS; and
2. They required either initial ventilatory support for more than 3 days or required reintubation.

Statistical Analysis

Clinical characteristics of the two treatment groups were compared by means of Student's two-sample t test (age), Pearson's chi-square test (sex, race, and risk factors at entry) and Kruskal-Wallis test (number of lesions on admission). The Kruskal-Wallis test was used also to test for association between UGIH and gastric lesion scores, and between organ system failures on entry and death. All statistical testing was two-sided at the 5% level of significance.

Results

One hundred twenty-seven patients meeting all entry criteria were randomized to receive either misoprostol (n = 63) or cimetidine (n = 64). The groups were clinically equivalent at entry (Table 3). The mean time between surgery and first dose of study medication was 4 days for each group (range, less than 1 day to 16 days). Outcome data comparing the patients receiving misoprostol with those receiving cimetidine demonstrated no statistically significant differences in final gastric endoscopy scores (p = 0.764), the development of UGIH (p = 0.179), the development of additional organ system failure (p = 0.073), or death (p = 0.292) (Table 4).

Therefore, because the two treatment groups were not shown to differ in any of the entry or outcome variables indicated above, data from the two groups were combined to determine the association, if any, between the development of stress lesions and the development of UGIH, additional organ system failures, and death.

Forty-four of the 127 patients died (35% mortality rate). All but two of these patients had organ failure in at least two systems at the time of death. Twenty-nine patients

TABLE 4. *Examination of Outcome Criteria by Treatment Group*

Outcome Criteria	Misoprostol (N = 63)	Cimetidine (N = 64)	Test Statistic	p
Final gastric score*			0.090†	0.764
1 (n = 24)	11/56 (20%)	13/55 (24%)		
2–4 (n = 65)	34/56 (61%)	31/55 (56%)		
>4 (n = 22)	11/56 (20%)	11/55 (20%)		
Met UGIH criteria (n = 10)	7/63 (11%)	3/64 (5%)	1.806‡	0.179
Additional organ system failure (n = 39)	24/63 (38%)	15/64 (23%)	3.206‡	0.073
Died (n = 44)	19/63 (30%)	25/64 (39%)	1.112‡	0.292

* Patients who did not undergo a second endoscopy were excluded.

† From Kruskal-Wallis test.

‡ From Pearson's chi square test.

UGIH, upper gastrointestinal tract hemorrhage.

died within 14 days of the first dose of study medication, and the other 15 died more than 20 days after the first dose. The time between surgery and the first dose (approximately 4 days) did not affect survival ($X^2 = 0.541$, $p = 0.462$).

Of the 127 patients, 10 (8%) met criteria for UGIH secondary to stress lesions, from 3 to 14 days after the first dose of study medication. None of the patients who developed UGIH had less than 10 stress lesions (combined gastric and duodenal lesions) when they hemorrhaged, and all but one of these patients had a preponderance of lesions in the stomach (Table 5). Four of the patients who went on to bleed were initially without lesions (score of 1) or showed healing (decreased their gastric score by at least one grade) at the 72-hour endoscopy. All four of these patients developed multiple new lesions at subsequent endoscopies. One additional patient had UGIH 9 days after the last dose of study medication.

Twenty-two of 111 patients (20%) who had a follow-up endoscopy demonstrated more than 10 gastric lesions (lesion score greater than 4) on repeat examination (Table 5). This was considered clinically significant evidence of diffuse gastritis. There were 36 patients with 6 to 10 gastric lesions at entry, which was the maximum number of lesions allowed (Table 3). When these patients were re-endoscoped, 13 (36%) demonstrated fewer lesions (*i.e.*, decreased their gastric score), eight (22%) showed no change, 11 (31%) developed more lesions (*i.e.*, increased their gastric score), and four (11%) could not be re-endoscoped (two of these patients had died). When patients were stratified by the results of their worst gastric endoscopic score (Table 5), the risk of developing significant UGIH was strongly associated with the number of gastric stress lesions developed ($p < 0.001$).

Five of the ten patients who met the criteria for UGIH died, but death was not temporally related to the hemorrhage (mean interval between bleeding and death, 9.6 ± 5.0 days). When bleeding status at the time of study termination was reviewed for the 127 patients, there was not a significant association between known UGIH and death (5 of 127; $p = 0.288$). There were 34 patients, however, who did not undergo a final endoscopic evaluation at the time of study withdrawal ($n = 10$) or at the time of death ($n = 24$), although they may have had a 72-hour endoscopy. These 34 patients could not be evaluated for UGIH because endoscopic confirmation of a bleeding source was required. None of these 34 patients, however, showed any of the three clinical signs of bleeding. Therefore, they were classified as having an unknown bleeding outcome. In the group of 24 patients who died before a second endoscopic examination could be performed, two patients had extensive UGI tract ulcerations and blood present at autopsy. When the remaining 93 patients who had an endoscopy at study termination were examined, there was a significant association observed between UGIH and death (5 of 93; $p < 0.05$). There were significantly ($p < 0.001$) more patients with an unknown bleeding outcome in the group who died (24 of 44, 55%) when compared with the group who did not die (10 of 83, 12%). Therefore, it is possible that the significant association for known UGIH and death for the 93 patients who had an endoscopy at study termination would be nonsignificant if the bleeding outcomes of a large fraction of the 24 patients who died with unknown bleeding outcome were known to be negative.

TABLE 5. *Relationship Between UGIH and Gastric Lesions*

	Met Criteria for UGIH	
Highest Gastric Score at Follow-up Endoscopy	Yes ($n = 10$)*	No ($n = 101$)
1	0	20
2	0	12
3	1†	42
4	1	13
5	3	2
6	4	7
7	1†	5

Chi square (Kruskal-Wallis) = 14.840
$p < 0.001$

* Follow-up endoscopy for these patients was when UGIH occurred.
† Duodenal mucosal score of 7.
UGIH, upper gastrointestinal tract hemorrhage.

Patients who had a prior history of UGIH or peptic ulcer disease were not excluded from this study as long as their initial endoscopic examination did not demonstrate mucosal damage more severe than 10 gastric or duodenal lesions. Six patients had a history of outpatient ulcer treatment, one patient had a history of a UGIH, and one patient had a history of bloody NG drainage. Four of these eight patients died (nonsignificant association with death, $X^2 = 0.889$, $p = 0.346$). One of the patients who died also met criteria for UGIH during study participation.

Sixty-nine patients (54%) in this study had MSOF at entry (Table 6). The presence of renal failure ($n = 25$), coagulopathy ($n = 29$), or hepatic failure ($n = 23$) at entry were each significantly associated with death, (64%, $p < 0.001$; 62%, $p < 0.001$; and 57%, $p < 0.02$, respectively). Additionally, the number of organ system failures at entry was significantly associated with death ($p < 0.001$).

Thirty-nine patients (31%) in this study developed 57 additional organ system failures not present at study entry. The development of either hepatic (14 of 104 patients at risk) or renal (22 of 102 patients at risk) failure was usually fatal (71% and 59%, respectively). The development of coagulopathy was less common (7 of 98 patients at risk) and associated with a 43% mortality rate. Eight of the

TABLE 6. *Association Between Organ System Failures and Death*

No. of Organ System Failures at Entry*	Died (n = 44)	Survived (n = 83)
1	11†	47
2	16	29
3	12	6
4	5	1

Chi square (Kruskal-Wallis) = 18.08
$p < 0.001$

* Failures in addition to mechanical ventilatory support and hypotension or sepsis.

† Had both hypotension and sepsis at entry.

thirty-two patients who did not have sepsis at entry developed sepsis during the study, and five (63%) of these patients died.

Fourteen patients were classified as having ARDS at the time of study entry. Six of these patients (43%) died. Ten other patients developed ARDS during study participation, and nine of these (90%) died. Of the 103 patients who did not have ARDS, only 29 (28%) died. Therefore, the presence of ARDS was significantly associated with death ($X^2 = 15.87$, 2 *df*, $p < 0.001$).

Discussion

This report examined postoperative patients who required ventilatory support and experienced an episode of either hypotension or sepsis, to assess the associations among the development of UGIH, diffuse gastritis, organ system failure, and death. Overall, only 8% of these patients developed UGIH, and this was significantly associated with the number of gastric lesions they developed. Of the 111 patients who underwent at least one follow-up endoscopy, 22 (20%) developed diffuse gastritis, and eight of these patients (36%) had a UGIH (Table 5). No patients required surgical intervention. This implies that although stress lesions are common in critically ill patients, hemorrhage requiring surgical treatment is rare when prophylaxis regimens are used.

Very few studies of critically ill patients have included multiple endoscopic evaluations. This is the first study to demonstrate that UGIH can develop in patients after interim endoscopy (72 hours after the initiation of prophylaxis) has shown that the gastric mucosa is either free of lesions or improving (*i.e.*, the number of lesions has decreased). The interpretation of this information must be made in light of the entry criteria for the study, which by design excluded patients who had already developed lesions or bleeding. This also may mean that studies that claim to identify patients not in need of prophylaxis on the basis of short-term evaluation may miss some patients who continue to be at risk.

The observed bleeding rate of 8% falls within the range of previously published reports examining patients given prophylaxis,[4-8] although few studies have examined a similar patient population. The expected rate of bleeding in groups receiving placebo in other studies ranges from 5% to 21%.[1,2,8] Despite the absence of overt gastrointestinal hemorrhage on entry to the study and the administration of prophylaxis, 41% of these patients (45 of 111) increased their gastric mucosal scores by at least one grade. Although there are some groups of patients in whom prophylaxis has legitimately been questioned,[9] patients with MSOF clearly needed prophylaxis to prevent gastrointestinal hemorrhage and the expensive evaluation and acute treatment such hemorrhage initiates.

This study confirms previous work identifying the stomach as a primary target organ in stress.[8,10,11] Only five patients had duodenal lesions on entry, and three of the four who had a second endoscopy improved (the other patient's status did not change). Of the two patients with late developing duodenal ulcers, one also had a gastric ulcer that was bleeding and a history of ulcer disease. The other patient had gastric erosions that were bleeding.

Published rates of pneumonia in ICU patients requiring mechanical ventilation have ranged from 10% to 34%.[4,5] Although ventilator dependence was an admission criterion for this study, ARDS was observed in 24 (19%) of the patients, 14 at admission and 10 who developed ARDS during the study (9% of the patients at risk). This rate is lower than prior reports[4,5] of pneumonia rates of up to 35% in patients receiving agents that raise pH; this may be because other studies included patients regardless of expected survival, whereas this study excluded patients who were not expected to survive at least 14 days. Additionally, this study did not prospectively collect information relevant to changes in each patient's pulmonary status and therefore had to rely on the reporting of the development of pneumonia or ARDS as an adverse event. In these patients, when a worsening of pulmonary status was reported, it was significant; 9 of the 10 patients whose pulmonary status worsened, died.

Finally, gastric pH was not measured in our patients, which makes it impossible to know how effective these treatments were in raising gastric pH and whether patient values correlated with either the development of UGIH or pneumonia. The dose of cimetidine used in this study does not routinely keep pH above 4 in critically ill patients [11] The dose of misoprostol used in these patients kept mean gastric pH above 4 in a prior group of 141 surgical ICU patients, but intubation and sepsis or hypotension were not required for inclusion in that study.[12] Sepsis has been correlated with lower gastric pH values and a high incidence of UGIH in other studies.[1,11] It is therefore possible that the lower rate of pulmonary problems seen in this study was due to prophylaxis regimens that did not routinely raise gastric pH above some critical value where pneumonia is more likely to occur.

The science of outcome prediction in the critically ill patient is relatively new and still inexact. Techniques for stratification often have been poorly applied or simply not used at all. Even when stratification criteria such as the APACHE II score have been used to study outcome,[5] the inclusion of many different types of patients (*i.e.*, medical and surgical admissions) does not allow outcome prediction because equations are disease specific.[13] This study examined a relatively homogenous group concentrating on postoperative patients without head injuries who were thought to be on the brink of the development of MSOF. In the patients in this study, the risk for the development of hemorrhage was similar to the risk for the development of ARDS. Any additional organ failure can push this type of patient over the brink.

Thirty-five per cent (35%) of the study population died, with all but two patients having MSOF. Death was significantly associated with the total number of organ system failures at entry and especially with the presence of hepatic failure, renal failure, or coagulopathy. Multiple system organ failure has become the most common cause of both prolonged stays and deaths in surgical ICUs in the last decade.[14,15] Techniques to better support organ function are desperately needed to reverse this trend. It seems essential to try to prevent stress lesions in patients with MSOF because even with prophylaxis, 41% of these patients develop more lesions, and lesion number correlates with the risk of UGIH.

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Reduction in Biliary IgA After Burn Injury

Role of Diminished Delivery via the Thoracic Duct and of Enhanced Loss From the Systemic Circulation

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The concentration of biliary IgA is greatly reduced after scald burn injury in the rat, thereby contributing to a deficiency in upper intestinal immune defense. This reduction in biliary IgA might have several explanations, including failure of the transhepatic transport of polymeric IgA (pIgA) from the circulation, decreased delivery of pIgA to the hepatocyte, or decreased local synthesis of IgA in the liver. The authors examined whether burn injury reduces circulating pIgA available for delivery to the hepatocyte. In initial studies, they demonstrated that burn injury induces a decrease in circulating pIgA in bile-duct–ligated rats. They then sought to determine whether this decrease in pIgA was due to increased loss from the circulation or to a decreased supply of pIgA to the circulation through the thoracic duct. After injection of purified ^{125}I-pIgA into bile duct-ligated rats, radioactivity was removed more rapidly from the circulation of burn-injured compared with control rats. The radioactivity localized in the skin and muscle at the site of burn injury. In another group of rats with patent bile ducts, the thoracic duct was cannulated and lymph collected for 12 hours. The total amount of IgA protein in lymph was found to be reduced in burn-injured compared with control animals. Thus, burn injury is accompanied by reduced circulating pIgA, which may be attributed to its enhanced loss from the circulation and to decreased delivery of pIgA from the intestinal mucosa to the systemic circulation via the thoracic duct.

BURN-INJURED PATIENTS are at risk of developing systemic infection related to bacteria translocating from their gastrointestinal tracts.[1] Deitch and Berg[1] suggested three mechanisms that contribute to the induction of bacterial translocation: (1) disruption of the normal indigenous microflora of the gut, (2) physical or functional disruption of the intestinal mucosal barrier, and (3) impaired immune defense.[2–4] Secretory immunoglobulin A (IgA) is an important component of immune defense in the intestinal lumen and on mucosal surfaces.[5] Secretory IgA in bile may account for up to 90% of the upper intestinal IgA in the rat and thus may contribute to the mucosal defense of the foregut.[6]

In a previous study, we demonstrated that the amount of IgA secreted into bile was reduced 75% to 90% 18 hours after burn injury.[7] This finding may be explained by a decrease in receptor-mediated transfer of polymeric IgA (pIgA) across the hepatocyte to bile[5] or by a decrease in supply of circulating or locally synthesized pIgA available for transport by the hepatocyte.[8,9] In the present study, we tested whether supply of circulating pIgA to the liver changes after thermal injury.

Methods

Iodination of IgA and Preparation of ^{125}I-pIgA

IR22 IgA myeloma protein (Zymed, San Francisco, CA) was radiolabeled with ^{125}I (New England Nuclear, Boston, MA) by the chloramine T method.[10] The radiolabeled protein had an approximate specific activity of 2

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to 4 μCi/μg. Preparation of the pIgA fraction from total IgA was performed by gel permeation chromatography using a Bio-Gel A-1.5m (fine) (BioRad, Richmond, CA) column (1 × 120 cm). The pIgA fraction was dialyzed against phosphate (0.01 M)-buffered saline, pH 7.4, for 18 hours at 4 C. Thereafter, 95% of the radioactivity in the pIgA fraction was precipitable in a final concentration of 10% trichloroacetic acid (TCA).

Induction of Burn Injury

Female CD-1 rats (Charles River Breeding Laboratories, Wilmington, MA) weighing 170 to 230 g were used in this study and were maintained in accordance with the guidelines contained in NIH Publication No 85-23. Experimental protocols were approved by the Subcommittee on Animal Care, Committee on Research, Massachusetts General Hospital.

Rats were subjected to sham treatment or burn injury.[7,11] Under ether anesthesia, the backs of animals were shaved and approximately 20% to 30% of the body surface was exposed to boiling water for 15 seconds. This treatment produced a full-thickness injury that appeared to be pain free, presumably because cutaneous nerve endings were destroyed. Sham-treated rats were anesthetized with ether and shaved. Both control and burn-injured rats were injected intraperitoneally with 10 mL normal saline solution immediately after injury or sham treatment.

Effect of Burn Injury on Endogenous Circulating IgA Protein

The effect of burn injury on the levels of circulating IgA protein was examined in rats whose bile duct was ligated to prevent the rapid secretion of pIgA into bile.[12] The bile duct was ligated under light ether anesthesia through a midline laparotomy. The animals were allowed to recover and received food and water. Twenty-four hours after surgery, burn injury or sham treatment was performed. Blood was obtained from the retro-orbital venous plexus before bile duct ligation, 24 hours after bile duct ligation (before thermal injury or sham treatment), and 24 hours after experimental treatment. Total IgA protein was measured in serum by radioimmunoassay according to the method of Sullivan and Allansmith.[13]

Effect of Burn Injury on Loss of Exogenous Labeled pIgA From the Circulation and Localization in Tissues

In a second series of experiments, the removal of ^{125}I-pIgA from the circulation was examined 24 hours after bile duct ligation. Radiolabeled pIgA (2.7 to 3.2 × 10^6 cpm; 350 to 700 ng protein in 0.5 mL phosphate-buffered saline [PBS] containing 1% normal rat serum) was injected into the femoral vein. Two minutes after the injection, blood was obtained from the retro-orbital venous plexus, and the rats then were subjected to thermal injury or sham treatment. Additional blood samples were subsequently obtained at 0.5, 3, 6, and 24 hours. The radioactivity in serum from these samples was determined and divided by the radioactivity present at 2 minutes to obtain the fraction of radioactivity remaining in the circulation at each time point. The radioactivity in the serum was characterized by precipitation in a final concentration of 10% TCA.

Because rapid fluid loss from the intravascular compartment is expected after thermal injury and is reflected by an increase in hematocrit,[14] the hematocrit was determined at 0.5, 3, 6, and 24 hours after treatment. We assumed that the erythrocyte mass is constant during the first 8 hours after burn.[14] To correct for the changes in plasma volume after thermal injury, the fraction of radioactivity in the circulation remaining at each time point after injury was divided by the hematocrit. The plasma volume was estimated at 24 hours after thermal injury or sham treatment in bile duct-ligated rats by the Evans blue dye dilution method.[15] Evans blue dye (Sigma, St. Louis, MO), 2 mg/kg body weight in 400 μL PBS, was injected intravenously. Blood was obtained 2 minutes later by cardiac puncture. The optical density of Evans blue dye in plasma diluted 1:3 in PBS was measured at 625 and 740 nm. The results were compared with those of Evans blue dye solutions of known concentrations. Interference due to hemoglobin or turbidity due to lipemia was corrected by Hamilton's equation based on absorption measurements made at 740 nm.[16]

The localization of radioactivity in tissues of treated rats was examined in a separate group of rats. Twenty-four hours after ligation of the bile duct, animals were injected with ^{125}I-pIgA and then subjected to burn injury or sham treatment. One hour and 24 hours after the injection of the ^{125}I-pIgA, separate groups of animals were anesthetized with ether and perfused with 120 mL heparinized (1 U/mL) saline solution to remove intravascular ^{125}I-pIgA from the animal. The burn-injured skin, liver, shaved normal skin, as well as cutaneous (panniculus carnosus) and skeletal muscle from below the dorsal surface of sham-treated and burn-injured animals were removed and rinsed in PBS. Tissue radioactivity and weight were determined. The radioactivity per gram of tissue was expressed as a percentage of the total radioactivity injected.

Effect of Burn Injury on the Supply of Endogenous IgA to the Systemic Circulation via the Thoracic Duct

To determine the amount of IgA delivered to the circulation via the thoracic duct, lymph was collected from the thoracic duct over a 24-hour period. Under light ether anesthesia, the thoracic duct was cannulated[17] with Silastic tubing (Dow Corning #602-135, Dow Corning Corp., Midland, ME) placed into the subdiaphragmatic portion of the thoracic duct and tunneled to exit through the dorsal skin. After thermal injury or sham treatment, lymph was collected on ice for 12 hours from animals that had access to drinking water. The IgA protein concentration in lymph was measured by radioimmunoassay (RIA).[13]

Statistical Analysis

The data were evaluated using the Systat Program (Systat, Evanston, IL) and tested for significant differences by t test or Mann-Whitney *U* tests. The Bonferoni Equality Method[18] was used to compare ^{125}I-IgA clearance from the circulation in burn-injured and sham-treated rats. Graphs were plotted using Sigmaplot software (Jandel Scientific, Sausalito, CA).

Results

Effect of Burn Injury on Endogenous Circulating IgA Protein

To examine the effect of burn injury on circulating IgA, the IgA concentration in serum was measured before bile duct ligation, 24 hours after bile duct ligation and finally 24 hours after burn injury or sham treatment. In 14 rats, the concentration of IgA in serum increased from 96 μg/mL to 1356 μg/mL in the 24 hours after bile duct ligation (Fig. 1). Thereafter, animals were divided into two groups that received either burn injury or sham treatment. At 24 hours after sham treatment, the IgA protein concentration had continued to increase, reaching a mean of 2277 μg/mL. In contrast, 24 hours after thermal injury, serum IgA concentration had decreased to 774 μg/mL, a value that was significantly different from the IgA concentration of the control ($p < 0.001$). To identify the molecular species of IgA affected by thermal injury induced 24 hours after ligation of the bile duct, serum from the burn-injured and sham-treated groups were subjected to gel permeation (Bio-Gel A-1.5 m) and the IgA concentration of the eluted fractions was determined by RIA. Immunoglobulin A was found predominantly in fractions containing protein with a molecular weight greater than 320,000 daltons (data not shown) in both groups.

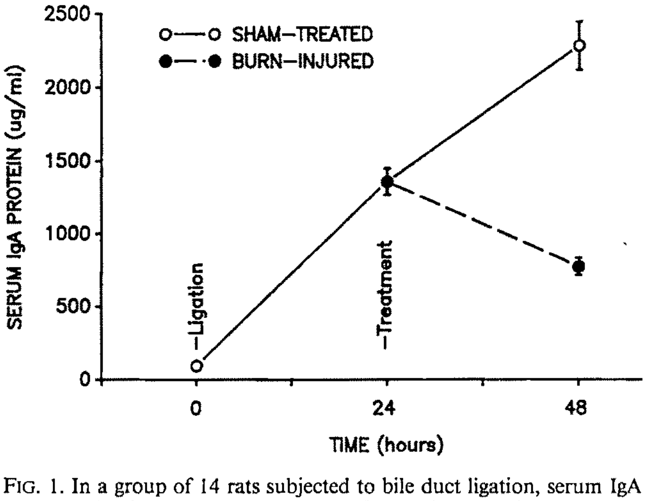

FIG. 1. In a group of 14 rats subjected to bile duct ligation, serum IgA concentration increased by 24 hr. Thereafter, half were subjected to sham treatment and half to burn injury. IgA concentration increased in the former and fell in the latter group. Each point represents the mean ± SEM.

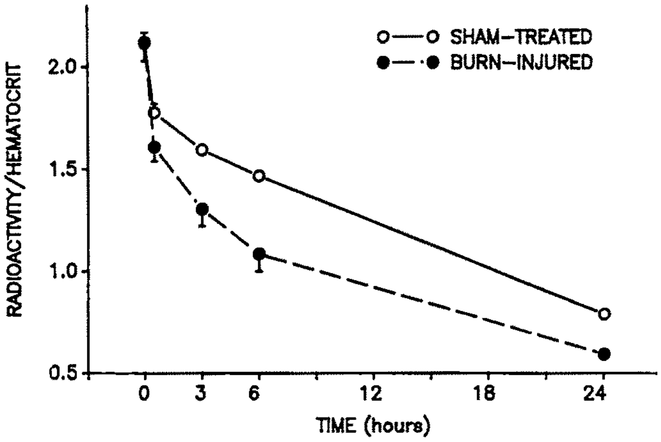

FIG. 2. Clearance from the circulation of ^{125}I-pIgA injected intravenously immediately before thermal injury or sham treatment in bile duct–ligated animals. The fraction of radioactivity remaining in the circulation at 0.5, 3, 6, and 24 hr after thermal injury has been corrected for hematocrit to adjust for changes in plasma volume. Five animals were tested after sham treatment and six after thermal injury. Mean ± SEM are indicated at each time interval. Significantly increased loss of radioactivity from the circulation was noted ($p < 0.03$ by two-sided Bonferoni t test) after thermal injury.

Effect of Burn Injury on Loss of IgA Protein From the Circulation

The fraction of radioactivity remaining in the circulation after burn injury (corrected for changes in hematocrit) decreased more rapidly in the burn-injured than in the sham-treated animals; the differences at 24 hours were significant at $p < 0.03$ after correction for multiple comparisons by the Bonferoni Equality method[18] (Fig. 2). To determine whether the radioactivity in the circulation was protein bound, precipitation with TCA was performed. The radioactivity in serum obtained at 24 hours from either seven burn-injured or six sham-treated rats was 96.3 ± 1.7%, and 95 ± 2.2% TCA precipitable, respectively. To confirm that the difference in clearance of radioactivity from the circulation was not related to differences in plasma volume, plasma volume was measured by the dye dilution technique[16] at 24 hours after thermal injury or sham treatment. The plasma volume was 3.4 ± 0.08 mL/100 g in sham-treated and 3.7 ± 0.12 mL/100 g in burn-injured animals (not significant).

Localization of Radioactivity in Tissues

To identify the sites at which ^{125}I-pIgA might be lost from the circulation in burn-injured rats, the radioactivity in skin, muscles, and liver obtained at 1 and 24 hours after injury was assessed. At 1 hour after injury, burn-injured skin had a ninefold and the cutaneous muscle layer had an eightfold increase in radioactivity compared with the skin ($p < 0.001$) and cutaneous muscle layer ($p < 0.001$) of the sham-treated animals (Fig. 3A). In the latissimus dorsi muscle, the radioactivity was 2.5-fold increased in burn-injured rats, but the difference between this group and the controls was not significant. Contrary to the burn-injured skin and cutaneous muscle layer, radioactivity in the liver was not significantly different after sham treatment or burn injury (Fig. 3A).

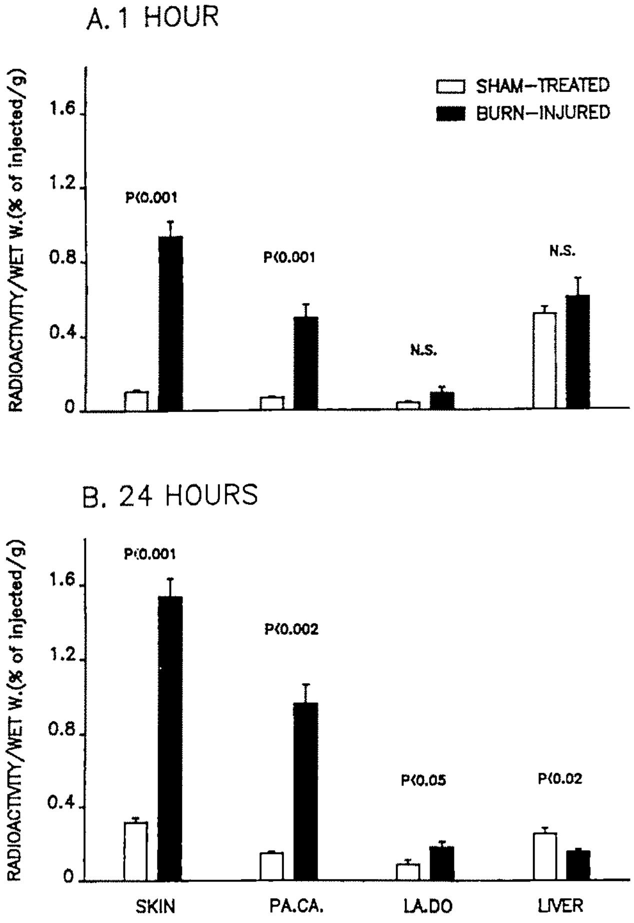

FIG. 3. Localization of radioactivity in skin, muscle, and liver at (A) 1 hr and (B) 24 hr after thermal injury or sham treatment. The radioactivity is expressed as percentage of injected radioactivity corrected for sample wet weight. Each bar represents the mean ± SEM for (A) n = 8 animals and (B) n = 5 animals after sham treatment and for n = 6 animals after burn injury. PA.CA., panniculus carnosus; LA.DO, latissimus dorsi.

TABLE 1. *Endogenous IgA in Thoracic Duct Lymph*

Collection Period (hr)	Group	Volume (mL)	IgA Concentration (μg/mL)	Amount of IgA (μg)
0–12	Sham treated (n = 3)	8.8 ± 0.6*	327 ± 60	2703 ± 772
	Burn injured (n = 5)	3.5 ± 0.2 p < 0.03	324 ± 55 NS	1055 ± 110 p < 0.03

* Mean ± SEM.

At 24 hours, the burn-injured skin had a fivefold increase in radioactivity compared with the skin of sham-treated rats ($p < 0.001$); the cutaneous muscle layer of burn-injured rats had a sixfold increase ($p < 0.002$) (Fig. 3B). In the latissimus dorsi muscle of burn-injured rats, the radioactivity was twofold increased ($p < 0.05$). In contrast, the radioactivity in the liver was significantly increased in the sham-treated compared with the burn-injured animals ($p < 0.02$).

Effect of Thermal Injury on Supply of IgA Delivered to the Circulation via the Thoracic Duct

To test for the effect of thermal injury on the supply of IgA delivered by the thoracic duct, the duct was cannulated and the rats then were subjected to sham treatment or burn injury. The volume of lymph collected during the 12 hours after treatment was significantly reduced in the burn-injured rats ($p < 0.03$). The concentration of IgA in the lymph was not different in the two groups. The total amount of IgA (product of volume × concentration) was reduced in the burn-injured compared with the sham-treated rats ($p < 0.03$) (Table 1).

Discussion

We previously demonstrated a large reduction in the amount and concentration of IgA protein in bile after burn injury in the rat.[7] This loss of biliary IgA, and consequently of upper intestinal IgA, might be explained by reduced transport of pIgA across hepatocytes into bile, by decreased local synthesis of IgA in the liver, or by decreased supply of pIgA to the liver. The latter possibility was suggested by the previous observation that circulating total IgA and pIgA were decreased after thermal injury.[7] In the present study, we extended these observations and probed the mechanism accounting for the diminished supply of IgA to the liver. We prevented loss of pIgA from the circulation by the transhepatic route by ligating the bile duct and tested the effect of burn injury on the concentration of endogenous serum IgA in these animals (Fig. 1). The concentration of serum IgA before and 24 hours after ligation was similar to that reported by other investigators.[12,19] After an additional 24 hours, rats subjected to sham treatment showed a further increase in serum IgA, whereas after burn injury there was a significant decrease in serum IgA in the bile duct-ligated animals. This decrease in serum IgA might reflect enhanced loss from or decreased supply of IgA to the circulation.

Harms et al.[20] demonstrated that burn injury was accompanied by a loss of vascular integrity, resulting in rapid transcapillary passage of proteins having a molecular size up to at least 340,000 daltons. Monomeric and dimeric IgA thus may leak from blood vessels in the injured animal. In control and burn-injured rats injected with ^{125}I-pIgA, we compared the radioactivity remaining in the skin and muscle layers of the burn-injured area, as well as the liver. One hour after burn injury, the radioactivity was significantly increased in the skin and cutaneous muscle layer of the burn site compared with the skin and muscle layer at the same site in sham-treated animals. The amount of radioactivity found in the tissues of burn-injured rats at 24 hours was greater than at 1 hour, suggesting that the increased vascular permeability persisted for some or all of that time. There was no significant difference between control and burn-injured rats in accumulation of radioactivity in the liver at 1 hour. The larger amount of radioactivity in the liver at 24 hours in sham-treated as compared with burn-injured animals may reflect greater persistence of radiolabeled pIgA in the circulation in these animals, which affords greater opportunity for uptake by the liver. The decrease in total radioactivity in liver of both groups during the interval between 1 and 24 hours may reflect intracellular breakdown and release of radioactivity from ^{125}I-pIgA.[21]

Manning et al.[8] demonstrated that drainage of lymph from the thoracic duct of rats by cannula resulted in a 60% reduction in the concentration of IgA in the circulation and a 75% decrease in the concentration of IgA in bile. We found that the concentration of IgA in thoracic duct lymph obtained during the 12 hours after cannulation was about 0.3 mg/mL, and that it was the same in burn-injured and sham-treated rats. These values compare with 1.6 mg/mL and 0.7 mg/mL reported by Manning et al.[8] and Vaerman et al.,[22] respectively, for normal rats. Although of comparable magnitude, the differences in IgA concentration between these and the present study may relate to differences in age or strain of rats, or to assay methods using standards with different ratio of monomeric to polymeric IgA. Sham-treated animals produced a mean of 8.8 mL lymph per 12 hours. This output is consistent with the range of 4 to 25 mL per 24 hours previously reported.[17,23,24] The difference in volume of thoracic duct lymph in the burn-injured group (3.5 mL per 12 hours) may relate to changes in systemic fluid balance during the first 12 hours after thermal injury or to decreased voluntary intake of water.[24] In the present experiments, IgA concentration in lymph and lymph volume were used to calculate the amount of IgA delivered by the thoracic duct in burn-injured and sham-treated rats. The amount of IgA delivered by the thoracic duct in the burn-injured group was reduced during the 12 hours of the collection period. Because the concentration of IgA in lymph was the same in the two groups of rats, it was the decrease in volume of lymph that was responsible for the decreased delivery of IgA.

In conclusion, an increased loss of pIgA from the circulation into the traumatized tissues and a decrease in supply of IgA delivered by the thoracic duct lymph to the circulation contribute to the decreased levels of IgA in the circulation after thermal injury and the decreased amount transferred into bile. Reduced delivery of IgA antibodies into the intestinal lumen by the bile may alter the immune defense of the gut in burned animals and may contribute to pathologic states such as those arising from bacterial translocation across the intestinal wall.[1]

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Clinicopathologic Studies on Perineural Invasion of Bile Duct Carcinoma

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To elucidate the clinical significance of perineural invasion on bile duct cancer, a clinicopathologic study was performed on 70 resected patients with bile duct carcinoma. The overall incidence of perineural invasion in the resected specimen was 81.4%. There seemed to be no correlation between perineural invasion and site, size of the tumor, and lymph node metastasis. A significant correlation was observed, however, between macroscopic type, microscopic type, depth of invasion, and perineural invasion. Perineural invasion index (PNI) was defined as the ratio between the number of nerve fibers invaded by cancer and the total number of nerve fibers with and without cancer invasion. Perineural invasion index was significantly higher at the center compared with the proximal and distal part of the tumor ($p < 0.001$). The 5-year survival rate for patients with perineural invasion was significantly lower ($p < 0.05$) than that for those without perineural invasion (67% *versus* 32%).

SPREADING OF TUMOR through the perineurium and its clinical significance has been described in a variety of head and neck,[1-6] prostate,[6-8] and pancreas[9-13] tumors. Previously, the perineural space was believed to be a part of the lymphatic system.[14,15] Contrary to this, later studies described this space as a separate channel from the lymphatic system and as an independent route of tumor metastasis.[6-8]

Many authors have emphasized the nerve dissection together with the tumor resection as a more radical approach to head, neck,[1,2,16,17] and pancreas head tumors.[9,10]

The perineural spread of bile duct cancer and its clinical significance, however, remain unclear. No extensive study has been conducted on bile duct cancer. The purpose of this present study is to evaluate the clinical role of perineural invasion in bile duct cancer, especially its influence on the prognosis and the mode of spread of this tumor through the perineurium.

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Materials and Methods

From January 1979 through September 1990, 94 cases of bile duct carcinoma were resected at the First Department of Surgery, Nagoya University Hospital. This study was conducted on 70 of the 94 resected cases on whom all necessary information was available; the remaining 24 cases were excluded from this study because of a lack of sufficient information. The age of the patients ranged from 32 to 82 years (mean, 57 years). Of the 70 patients, 48 (68.5%) were men and 22 (31.5%) were women. In this study, the term carcinoma of the hepatic hilus included lesions arising from the common hepatic duct, right, left, or both hepatic duct and intrahepatic bile duct cancer invading the hepatic hilus. The middle and lower bile duct cancers also were included, and the lesions arising from the papilla of Vater and the gallbladder were excluded from this study. All patients were precisely evaluated preoperatively, and the lesions were resected at the following surgical operations:

1. Bile duct resection only ($n = 2$)
2. Hepatectomy with bile duct resection ($n = 46$)
3. Pancreatoduodenectomy ($n = 18$)
4. Hepatopancreatoduodenectomy[18]($n = 4$)

After operation, the resected specimens were immediately processed first with normal saline and then with a mixture of equal parts of formalin. Resected specimen cholangiography was done for every case. Each then was washed, photographed, described, and then submersed into the formalin solution before further study. The fixed resected specimens were serially sliced in each 5 mm that corresponded with the cuts generated by the recent com-

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puted tomography (CT) scan. The blocks were taken from the slices processed through paraffin and the slides were prepared for microscopic study staining with hematoxylin and eosin. The perineural invasion was defined as tumor cells found in the perineural spaces and extending along them. Nerve fiber with or without perineural cancer invasion was calculated at least three places in each part of the tumor, and perineural invasion index (PNI) was calculated from the mean values in each part of the tumor according to the following formula:

$$\text{PNI} = \frac{\text{Number of nerve fiber invaded by tumor}}{\text{Total number of nerve fibers with and without tumor invasion}}$$

The PNI was calculated at the proximal end, the center, and the distal end of the tumor, and the grade of perineural invasion was made according to the PNI. Grade I means $\text{PNI} = 0.00$ (this group had no perineural invasion), grade II means $\text{PNI} < 0.70$, and grade III means $\text{PNI} \geq 0.70$ (this group had severe perineural invasion) (Fig. 1). Fol-

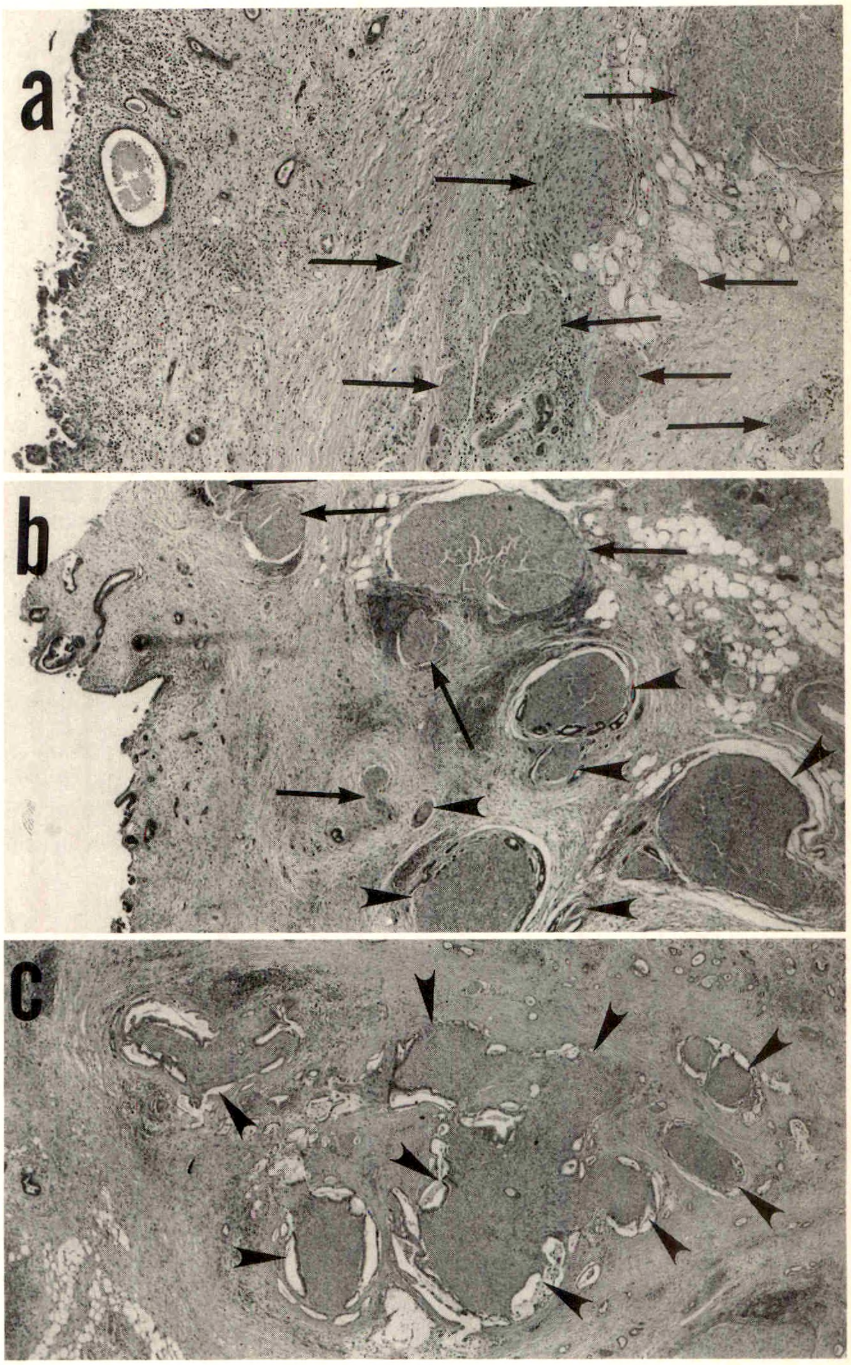

FIG. 1. The microscopic features of (a) PNI grade I bile duct cancer show no cancer cells in the perineural space (arrows). Invasion of many perineural spaces by cancer cells (arrowheads) and some of the perineural spaces without cancer invasion (arrows) can be seen in (b) PNI grade II bile duct cancer. Almost all of the perineural spaces are severely involved by cancer cells (arrowheads) in case of (c) PNI grade III bile duct cancer.

low-up information was available for all 70 patients for periods that varied from 9 months to 131 months, the average being 65.5 months. The Kaplan-Meier method was used to evaluate the survival rate. The statistical analysis was done by paired and nonpaired Student's t test, generalized Wilcoxon test, and chi square test.

Results

Operative Procedures

An operative procedure was selected according to the preoperative precise diagnosis. Curative operation was performed in 53 patients and noncurative resection in 17 patients. In case of bile duct carcinoma of the hepatic hilus, caudate lobe resection was included in all patients together with bile duct or liver resection according to our strategy of treating this carcinoma.[19]

Perineural Invasion Index in Bile Duct Cancer

To find out the frequency of perineural invasion in bile duct cancer and possible direction of spread of cancer through the perineural space, the PNI was calculated at the proximal, center, and distal part of the bile duct cancer (Table 1). This showed the distinct significant differences of PNI between the center of the tumor, and proximal or distal to the tumor ($p < 0.001$). Conversely, the distal PNI was significantly more than that of the proximal in carcinoma of the hepatic hilus ($p < 0.01$). There was, however, no significant difference between the proximal and distal site of the tumor in middle and lower bile duct cancer. These findings suggested that the most frequent site of nerve involvement by cancer was around the center of the tumor and could be disseminated either proximally or distally through the perineural space, but the distal dissemination was more frequent than proximal ($p < 0.01$).

Perineural Invasion and Location of Primary Tumor

Fifty-seven of the total seventy (81.4%) resected cases of bile duct cancer showed perineural invasion. It was observed in 42 of 52 (80.7%) of the carcinoma of the hepatic hilus, 7 of 8 (87.5%) of the middle bile duct cancer, and 8 of 10 (80%) of the lower bile duct cancer. From these findings, no significant conclusion could be drawn as to the relation between the primary site of tumor and perineural invasion.

The relation between the gross macroscopic feature of the lesion and perineural invasion is shown in Table 2. There was a statistically significant relation between the macroscopic type of the tumor and the presence of perineural cancer invasion ($p < 0.01$).

TABLE 1. *Perineural Invasion Index in Bile Duct Cancer*

Location of PNI Calculation	Location of Primary Lesion					
	Hepatic Hilus		Middle and Lower		Total	
Proximal	0.06 ± 0.04	*	0.02 ± 0.01	*	0.05 ± 0.05	*
Center	0.37 ± 0.31	†	0.35 ± 0.30	NS	0.36 ± 0.29	†
Distal	0.13 ± 0.09	*	0.01 ± 0.01	*	0.10 ± 0.11	*

Mean ± SD.
* $p < 0.001$.
† $p < 0.01$.
PNI, perineural invasion index.

TABLE 2. *Relation Between Gross Type of Lesion and Perineural Invasion*

Gross Type	Perineural Invasion	
	Positive	Negative
Papillary (n = 14)	6 (42.8%)	8 (57.2%)
Nodular (n = 22)	17 (77.2%)	5 (22.8%)
Nodular infiltrating (n = 10)	10 (100.0%)	0 (0.0%)
Infiltrating (n = 24)	24 (100.0%)	0 (0.0%)
Total (n = 70)	57 (81.4%)	13 (18.6%)

Statistically significant ($p < 0.01$).

Correlation Between Perineural Invasion and Histologic Type

Perineural invasion was less frequently observed in papillary adenocarcinoma than in the other histologic types (Table 3). These findings were suggestive of a correlation between the histologic type and perineural invasion. The statistically significant correlation was observed between the papillary and nonpapillary carcinomas ($p < 0.05$).

The relation between the depth of cancer invasion and perineural invasion is shown in Table 4. A distinct significant correlation can be found between the depth of cancer invasion and perineural invasion ($p < 0.01$). The

TABLE 3. *Correlation Between Perineural Invasion and Histologic Type*

Histologic Type	Perineural Invasion		
	Positive	Negative	
Papillary adenocarcinoma (n = 6)	3 (50.0%)	3 (50.0%)	
Well-differentiated adenocarcinoma (n = 22)	18 (81.8%)	4 (18.2%)	*
Moderately differentiated adenocarcinoma (n = 39)	33 (84.6%)	6 (15.4%)	
Poorly differentiated adenocarcinoma (n = 2)	2 (100.0%)	0 (0.0%)	
Adenosquamous cell carcinoma (n = 1)	1 (100.0%)	0 (0.0%)	

* $p < 0.05$.

TABLE 4. *Correlation Between Depth of Cancer Invasion and Perineural Invasion*

	Perineural Invasion	
Depth of Invasion	Positive	Negative
Mucosa (n = 3)	0 (0%)	3 (100%)
Fibromuscular layer (n = 4)	2 (50%)	2 (50%)
Adventitia (n = 2)	1 (50%)	1 (50%)
Subserosa (n = 46)	40 (87%)	6 (13%)
Serosal exposure (n = 9)	8 (89%)	1 (11%)
Invasion to other organ (n = 6)	6 (100%)	0 (0%)

Statistically significant ($p < 0.01$).
* $p < 0.001$.

perineural invasion was more frequently observed in tumors with invasion to or beyond the subserosal layer, whereas no perineural invasion was seen in mucosal tumors. Conversely, statistically more significant correlation was observed between the depth of invasion limited to the adventitial layer group and the depth of invasion to and beyond the subserosal layer group ($p < 0.001$).

Association of Perineural Invasion with Vascular, Lymphatic, and Lymph Node Involvement

Among the perineural invasion-positive patients, 49.1% showed lymph node metastasis, whereas 23% of the perineural invasion-negative patients had lymph node metastases (Table 5). This result suggested that there was no relation between the perineural invasion and lymph node metastasis. A significant association between the perineural invasion with vascular ($p < 0.001$) and lymphatic vessels ($p < 0.001$) involvement were observed, however.

Tumor Size and Perineural Invasion

Twelve of fifteen (80%) patients with a tumor equal and less than 2 cm in diameter showed perineural invasion. Of 55 patients with a tumor more than 2 cm in diameter, 45 (81%) disclosed perineural invasion. This finding seemed to show no relation between the perineural invasion and the size of the tumor.

TABLE 5. *Association Between Perineural Invasion with Vascular, Lymphatic, and Lymph Node Involvement*

	Perineural Invasion		
Cancer Involvement	Positive (%)	Negative (%)	
Vascular positive	49/57 (85.9)	4/13 (30.7)	$p < 0.001$
Lymphatic positive	54/57 (94.7)	6/13 (46.1)	$p < 0.001$
Lymph node positive	28/57 (49.1)	3/13 (23.0)	NS

Correlation Between Perineural Invasion and Local Recurrence

Eight of the 57 (14%) patients with positive perineural invasion showed local recurrence. No negative perineural invasion (0/13) patients had local recurrence, however. This finding was suggestive of a relation between local recurrence and perineural invasion. This was not statistically significant, however.

Survival

The 3-year and 5-year survival rates were 44% and 31%, respectively, for all 70 resected cases. The survival curve of patients (excluded four operative deaths) according to the presence or absence of perineural invasion showed that the survival rate of patients with perineural invasion was significantly lower than that of those without perineural invasion ($p < 0.05$) (Fig. 2). The 3- and 5-year survival rates for patients without perineural invasion are 80% and 67%, in contrast to that for those with perineural invasion: 41% and 32%, respectively. The survival curve of patients according to the grade of perineural invasion is shown in Figure 3. The patients with grade I perineural invasion had a significantly better survival when compared with grade II ($p < 0.05$) and grade III ($p < 0.01$) perineural invasion groups. Moreover, there were no 5-year survivors in the grade III group, whereas 67% survived in the grade I group.

Discussion

The surgical management of bile duct cancer is difficult, particularly in cases of carcinoma of the hepatic hilus. With the recent improvement of investigative and surgical techniques, the rate of curative resection of the carcinoma of the hepatic hilus has been increasing, with acceptable

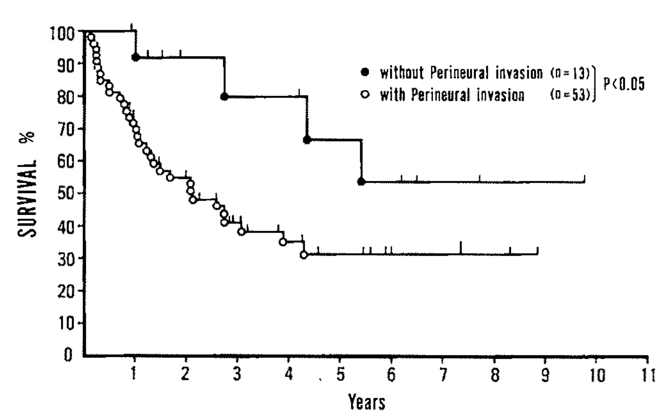

FIG. 2. The survival curves of the patients according to the presence or absence of perineural invasion excluding the four operative deaths. A statistically significant difference is seen between patients with and without perineural invasion ($p < 0.05$).

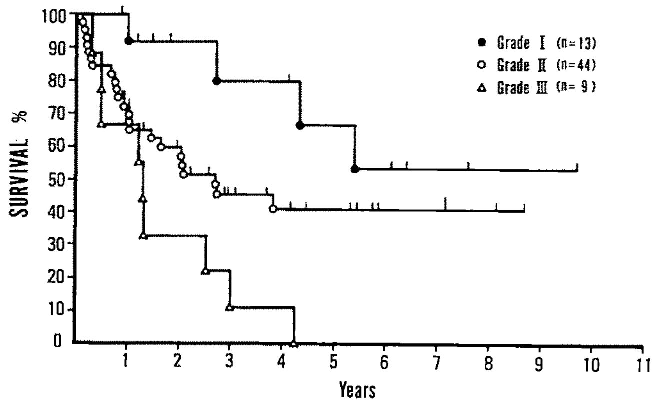

FIG. 3. The difference in survival distribution according to the grade of perineural invasion excluding the four operative deaths. Grade I shows significantly better prognosis compared with grade II and grade III (I *vs.* II, $p < 0.05$; I *vs.* III, $p < 0.01$; II *vs.* III, NS). The grade I lesion in 13 patients shows 80% 3-year and 67% 5-year survival rates, in contrast to 46% 3-year and 41% 5-year survival rates for 44 patients with grade II perineural invasion and 11% 3-year and 0% 5-year survival rates for 9 patients with grade III perineural invasion.

mortality rates.[19,20] Local recurrence, however, could be observed in some cases even after curative resection of this tumor.

Spreading of bile duct cancer may occur through any of the following ways: (1) direct invasion or extension, (2) seeding, (3) vascular, and (4) lymphatic permeation. There are few reports on the significance of the perineural spread in view of treatment. However, this has a great influence on survival of the patients, according to the observations from the present study.

Since the Ernst's[21] first report of tumor spread through the neural spaces, there have been reports on perineural spread of cancer at different situations.[1-17] Many authors[1,2,16,17] emphasized resection of the nerve together with a primary tumor as a more curative approach to prevent recurrence of the tumor as well as distal spread in head and neck tumor. Moreover, some authors[9,10] have suggested concomitant nerve tissue dissection together with celiac ganglionectomy as a more radical surgical treatment for carcinoma of the head of the pancreas. Others,[5,16] however, described that sometimes the spread of tumor was so distant through the perineurium that it was ignored at first observation but during the latter period of observation it became unresectable.

Many authors[14,15] had previously described that the tumor cells spread by embolism or permeation into the lymphatic channels of the perineurium. Contrary to that, recently many authors[6-8] described by light and electron microscopic studies that the perineural spaces were entirely different from lymphatic system and there was no connection between the perineurium and the lymphatic system. Moreover, they did not observe any lymphatic vessels in the nerve tissue.

Larson et al.[6] observed in an experimental study that the injected material (India ink) in the perineurium of the femoral, median, lingual, and hypoglossal nerves passed both proximally and distally. Our findings showed that the spread of tumor through the perineurium was significantly dominant in the distal direction of the bile duct in carcinoma of the hepatic hilus. This may be due to the fact that the intrahepatic perineural space is not so wide as the extrahepatic perineural space, which is the proximal part of the autonomic nervous system. Therefore, the tumor could be extended through the wider pathway more easily than through the narrow pathway; however, the tumor spread could be occurring in any direction.

Our findings suggested that there was a correlation between the depth of cancer invasion, macroscopic and microscopic type of tumor, and the perineural invasion. The perineural invasion was encountered more frequently when the tumors invaded the subserosal layer and beyond the subserosa. Moreover, a significant association with the perineural invasion and lymphatic and vascular invasion was encountered. This may be due to aggressive invasive behavior of the cancer. Our study showed no correlation between the perineural invasion and the occurrence of metastases to regional lymph node, the site and size of the tumor, and local recurrence. The present study concludes that spreading of the bile duct cancer does take place through the perineural space, and the surgeons should always keep their mind on this fact during managing the bile duct cancer.

Tompkins et al.[22] reported several prognostic factors regarding proximal bile duct carcinoma. They did not mention the perineural invasion as a prognostic factor for this tumor, however. White[23] denied the importance of perineural invasion on survival of bile duct cancer patients. Moreover, Beazly et al.[24] advocated that the nerve invasion was a very common finding in high bile duct cancer; however they could not find out any biologic significance of perineural invasion. Many authors,[1,3,25,26] however, have pointed out a significant correlation between perineural invasion and prognosis. They have stated that patients with positive perineural invasion implied a hopeless prognosis. The present study also showed a good correlation between the survival of patients and the perineural invasion. This shows that the 5-year survival rate was 67% of patients without perineural invasion, contrasting with 0% of patients with severe perineural invasion. This result strongly suggested that the perineural invasion has a profound impact on survival of the patient with bile duct carcinoma.

Therefore, we would like to emphasize the need of autonomic nerve fiber and plexus dissection around the hepatic and celiac arteries, portal vein, and sometimes right celiac ganglionectomy, together with the lymph nodes, lymphatic, and connective tissues dissection to eradicate the cancer tissue completely and perform the curative operation for bile duct cancer. We have been hoping to evaluate such an aggressive procedure in view of operative morbidity, mortality, and quality of life of the patients.

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Prognostic Value of Serum CA 19-9 Levels in Pancreatic Adenocarcinoma

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Thirty-eight patients with histologically proven pancreatic adenocarcinoma were investigated to establish the utility of serum CA 19-9 as a prognostic indicator. CA 19-9 assays were performed serially during the course of the disease. In four patients with negative Lewis blood type, the CA 19-9 levels remained essentially normal throughout the disease course. In the remaining 34 patients, (1) CA 19-9 levels were significantly lower in patients with tumor size no larger than 5 cm in diameter, and in patients with resectable tumors than in those with tumor size larger than 5 cm or with unresectable tumors ($p < 0.01$). 2) CA 19-9 levels dropped sharply after resection in all 11 resectable patients, whereas no significant change was found after laparotomy without resection. (3) The average survival time in seven patients whose CA 19-9 levels returned to normal after resection was significantly longer than in those four patients with postoperative CA 19-9 levels that decreased but did not return to normal (21.9 *versus* 8.7 months, $p < 0.05$). (4) In 6 of 11 patients who underwent resection, recurrent elevation of CA 19-9 preceded changes detectable by computed tomography or clinical examination by 2 to 9 months. (5) In 23 patients who died of pancreatic carcinoma, 15 (65%) had an obvious rise in CA 19-9 level before death. There was a correlation between the doubling time of the CA 19-9 serum level and survival time ($r = 0.5$, $p < 0.05$). Because it can be demonstrated that the reduction of tumor burden by resection lowers serum CA 19-9 levels, serum CA 19-9 levels may be a useful indicator of whether other forms of treatment such as radiation therapy or chemotherapy also reduce the tumor burden.

SINCE THE CA 19-9 monoclonal antibody was produced from a hybridoma cell line that was established by Koprowski et al.[1] in 1979, much has been written on its usefulness in patients with exocrine pancreatic adenocarcinoma.[2-5] There are limitations, however, on its use for the initial diagnosis of the disease.[6,7] Currently, attention is being focused on the utility of serum CA 19-9 in determining the prognosis of postoperative surgical patients with pancreatic adenocarcinoma and in monitoring postresection patients for recurrence of the disease.[8,9] It has been reported[10] that patients who are Lewis blood type negative (Le^{a-b-}) do not express the CA 19-9 antigen, and thus, a negative Lewis blood type may be seen in a significant number of pancreatic patients who lack elevated serum CA 19-9 levels.[10] The present study is a clinical evaluation of the value of serial measurements of serum CA 19-9 levels in determining prognosis in patients with pancreatic adenocarcinoma in patients that are Lewis blood type positive.

Materials and Methods

Between January 1987 and November 1990, 38 patients (22 men and 16 women) with histologically proven pancreatic adenocarcinoma were studied. Each patient underwent laparotomy, at which time the longest diameter of the tumor was recorded. The patients were divided into two groups according to the tumor size (group 1, tumor size ≤ 5 cm; group 2, tumor size > 5 cm). They were secondarily grouped by tumor resectability *versus* nonresectability. Serum CA 19-9 serum levels were determined serially by an immunoradiometric assay using the Centocor radioimmunoassay kit (Centocor, Inc., Malvern, PA). A value of 37 U/mL was used as the upper limit of normal[11] Serum samples were collected from the patients 1 or 2 weeks before operation and approximately 1 week, 1 month, and every 3 months after operation. For patients with serum CA 19-9 levels lower than 500 U/mL, Lewis blood type was tested using blood grouping serum Anti-Le^a and Anti-Le^b (Ortho Diagnostic Systems, Inc., Raritan, NJ). Additional follow-up studies included clinical examination, routine biochemical and hematologic profiles, and computed tomography (CT) scans at 3-month intervals after operation. The rate of the increase of CA 19-9 levels was evaluated in terms of doubling time, the

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time in days required for the CA 19-9 to double.[12] It was determined on the time axis between the two points that corresponded to the doubled serum CA 19-9 values.

Statistical Analysis

Determination of statistical significance of comparisons in CA 19-9 values was calculated using Mann-Whitney *U* test because of the skewness in the distribution of the data.[13] For comparisons in survival time, the Student's t test was employed. The correlation between doubling time and survival time was calculated by linear regression using the least square method.

Results

Patients Included in the Study

Of the 38 patients, 35 had one or more preoperative CA 19-9 determinations. The CA 19-9 levels ranged from <6 to 238,900 U/mL, the median being 330. Of the 35 patients, 22 had preoperative serum CA 19-9 levels lower than 500 U/mL. Of the 22, four were Lewis blood type negative. The four lowest CA 19-9 levels were found in Lewis-negative patients, including three normal values (<6, 9.2, 21, 45 U/mL). After excluding these four Lewis-negative patients, the median CA 19-9 level in the series was 360 U/mL.

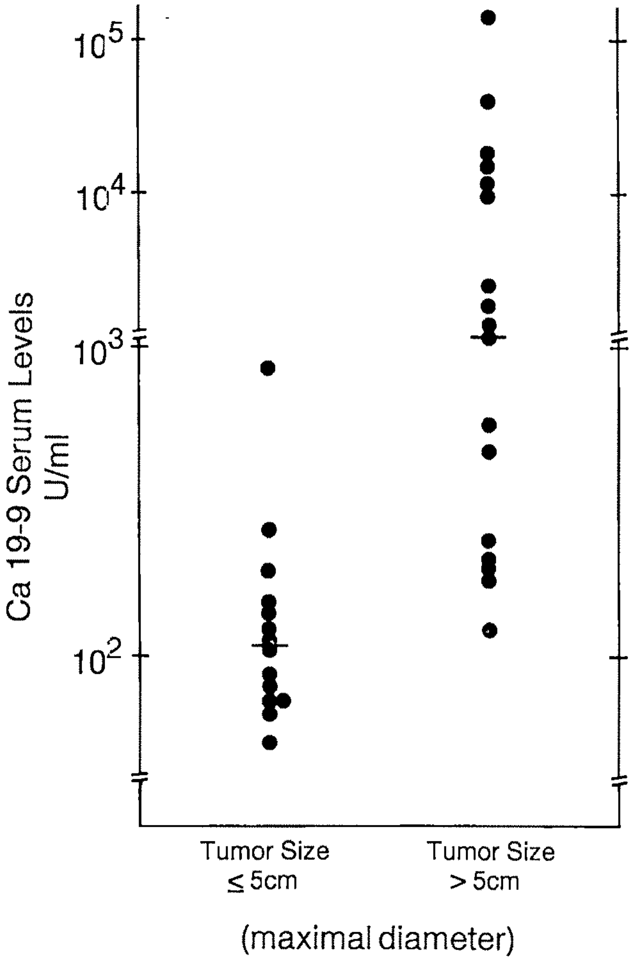

FIG. 1. Serum CA 19-9 levels in 14 patients with tumor sizes of 5 cm or less compared with 17 patients with tumor sizes greater than 5 cm. Data in this figure and in all subsequent figures were taken from patients with Lewis-positive blood. The bars represent median values ($p < 0.01$).

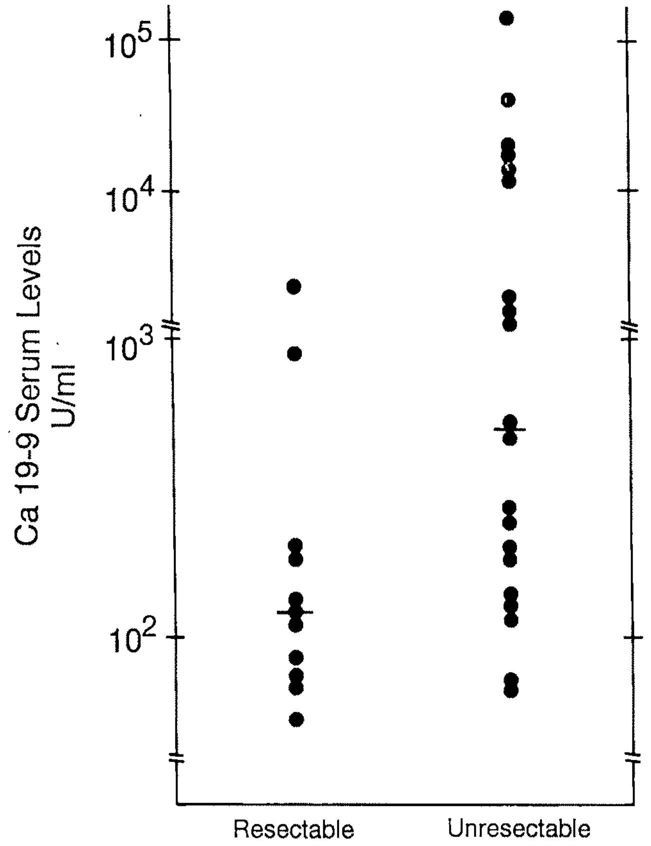

FIG. 2. Comparison of CA 19-9 serum levels between 11 patients with resectable disease and 20 patients with unresectable disease. The bars represent median values ($p < 0.01$).

Relation Between CA 19-9 and Tumor Size or Resectability

In 31 patients who were Lewis blood type positive and whose CA 19-9 titers were measured preoperatively, 14 had tumors with diameter ≤ 5 cm, 17 had tumors with diameter > 5 cm. As shown in Figure 1, the medians of serum CA 19-9 levels of these two groups were 120 U/mL and 750 U/mL, respectively. The difference were statistically significant ($p < 0.01$) in spite of the multiple overlaps of the CA 19-9 values between the two groups. As shown in Figure 2, similar results ($p < 0.01$) were obtained when the 31 patients were divided into resectable (n = 11, median of CA 19-9 = 130 U/mL) and unresectable (n = 20, median of CA 19-9 = 745 U/mL) groups.

Response to Tumor Resection

Fourteen of thirty-eight patients underwent a standard or radical pancreaticoduodenectomy, usually with intraoperative radiation. Of the 14 patients that underwent pancreaticoduodenectomy, 12 survived longer than 1 month and were included in the study. In those 12 patients, the serum CA 19-9 level decreased sharply over a 2-week period after resection except the one Lewis-negative patient whose preoperative CA 19-9 level had been normal (Fig. 3A). In 7 of the remaining 11 patients with positive Lewis blood type, the CA 19-9 levels fell to within the normal range. In four patients, after radical resection, the levels decreased but remained above normal. As a control group, 11 patients with unresectable tumors underwent simple laparotomy and biopsy. No significant changes in CA 19-9 levels were found after operation. There was, however, to a certain extent, a decrease in CA 19-9 level in seven of nine unresectable patients with obstructive jaundice after biliary decompression (Fig. 4).

Response of CA 19-9 to Recurrence or Metastasis

In 6 of the 11 Lewis-positive patients who survived "curative" resections, distant metastasis or local tumor recurrence was subsequently detected. The secondary elevation of the CA 19-9 level was detected 3 to 24 months after operation. These secondary elevations preceded detectable CT scan changes or clinical examination by 2 to 9 months (Table 1).

Prediction of Survival Time

In seven tumor-resectable, Lewis-positive patients with normal postoperative CA 19-9 levels, the average survival time was >21.9 months as shown in Figure 3A. Of these seven patients, four remain alive and well 13 to 29 months later with relatively stable, low levels of CA 19-9 and without any clinical evidence of recurrence or metastasis of the disease up to the time of this report. One showed a secondary elevation of CA 19-9 before hepatic metastasis was found by CT. In four patients whose CA 19-9 levels remained elevated after operation, the average survival time was 7.8 months, a significantly shorter time than the former group ($p < 0.05$) (Fig. 3B). Figure 5 shows the sequence of changes in CA 19-9 levels in two typical patients with different postoperative courses. In 26 patients who died of pancreatic cancer, three were Lewis-negative patients whose CA 19-9 remained a low value until death. Of the 23 Lewis-positive patients, 15 had an obvious rise in CA 19-9 level before death (65%). After a sudden rise in CA 19-9 levels, the patients' subsequent survival was approximately 2.9 to 13.8 times their CA 19-9 doubling time. A linear correlation ($r = 0.5$, $p < 0.05$) was established between these two times (Fig. 6).

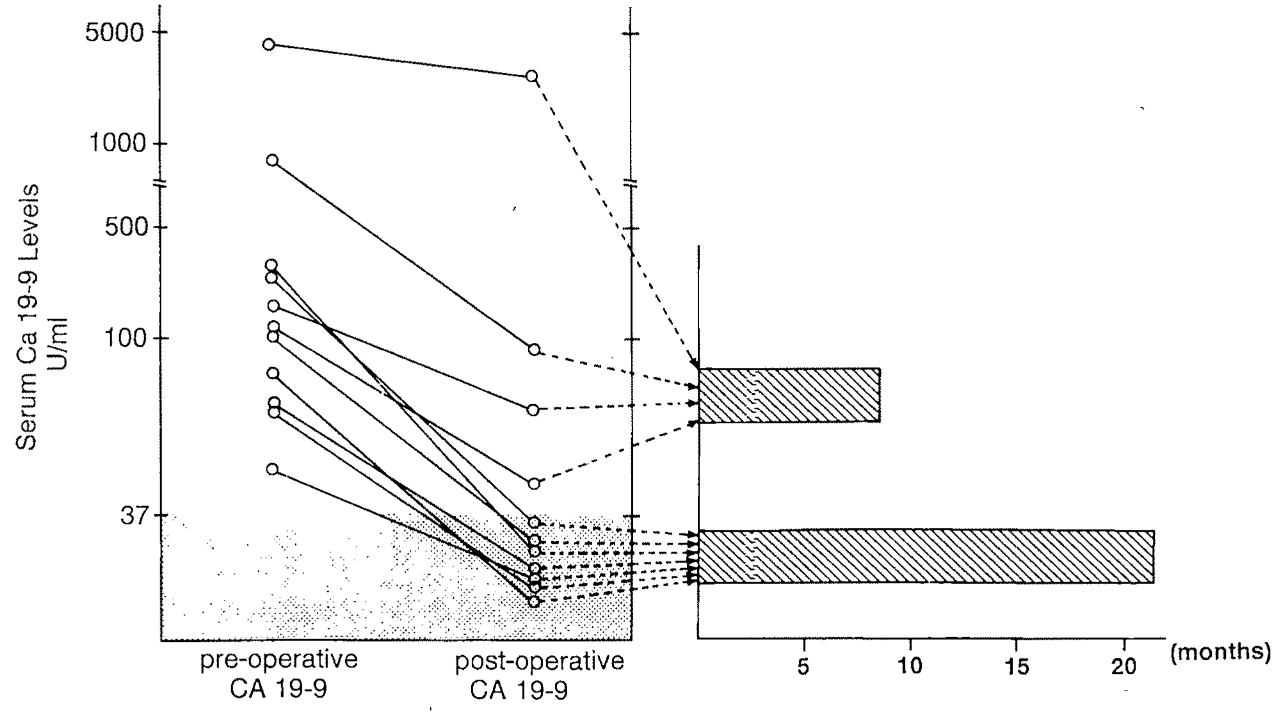

FIG. 3. (A, left) Changes in serum CA 19-9 levels in 11 patients who underwent resection of pancreatic carcinoma. Shaded area represents normal range of serum CA 19-9 levels. (B, right) Mean survival times of seven patients with normal serum CA 19-9 levels after operation *versus* four patients with elevated CA 19-9 levels.

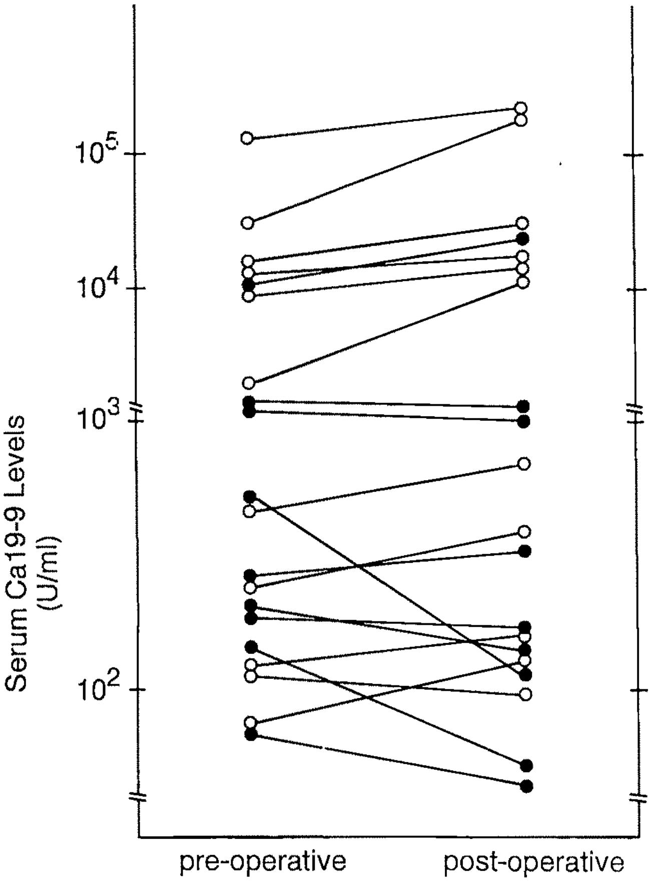

FIG. 4. Serum CA 19-9 levels before and after operation for unresectable pancreatic carcinoma in 9 patients who underwent biliary bypass for jaundice (closed circles) and in 11 patients without jaundice who underwent laparotomy (open circles).

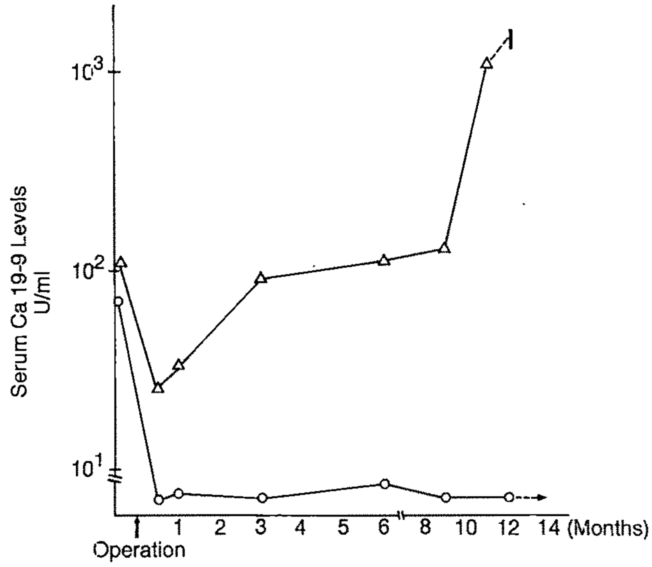

FIG. 5. Serum CA 19-9 levels in two typical patients with different courses of pancreatic carcinoma after tumor resection. Patient A (triangles), a 61-year-old man, died of liver metastasis at the time indicated by the vertical bar. Patient B (circles), a 50-year-old man, is alive and well.

Discussion

Numerous investigators have reported on the utility of CA 19-9 in early and differential diagnosis of pancreatic adenocarcinoma. The sensitivity (69% to 93%) and specificity (78% to 98%) reported in various series were quite encouraging.[1-3,14-16] Only a few reports, however, have appeared evaluating the utility of serum CA 19-9 determination in monitoring the course of the disease.[8,9] This study has evaluated the usefulness of monitoring patients with known carcinoma of the pancreas by serial CA 19-9 radioimmunoassay. Previous investigators have noted that an elevation of serum CA 19-9 can be a measure of tumor progression.[17,18] One of the important factors limiting the sensitivity of serum CA 19-9 assay is that some pancreatic cancers do not express this antigen to an appreciable extent. Exclusion of these patients is thus a prerequisite for the use of serum CA 19-9 antigen levels in the diagnosis and evaluation of the progress of the disease.

Studies have shown that subjects with the Le^{a-b-} blood group practically never produce CA 19-9 antigen.[10,19] The CA 19-9 epitope is a complex carbohydrate that is a sialated Lewis (Le^a) blood group antigen. The expression of the CA 19-9 epitope depends on the presence of the glycosyltransferase that sialates the Lewis antigen.[20] The

TABLE 1. *Lead Time of CA 19-9 Re-elevation vs. Clinical Evidence of Cancer Recurrence*

Patient	Age	Sex	Time of CA 19-9 Level Re-elevation (mo after operation)	Clinical Evidence of Cancer Progression: Time	Clinical Evidence of Cancer Progression: Examination	Results	Lead Time of CA 19-9 Assay (mo)
1	56	M	24	31	CT	Pulmonary metastasis	7
2	59	F	6	8	CT	Local cancer recurrence	2
					PE	Abdominal wall metastasis	
3	50	F	6	10	CT (−) Laparotomy	Hepatic metastasis	4
4	61	M	3	9	CT	Hepatic metastasis	6
5	67	M	12	21	CT	Hepatic metastasis	9
6	65	F	3	5	CT	Pulmonary metastasis	2

CT, computed tomography; PE, physical examination.

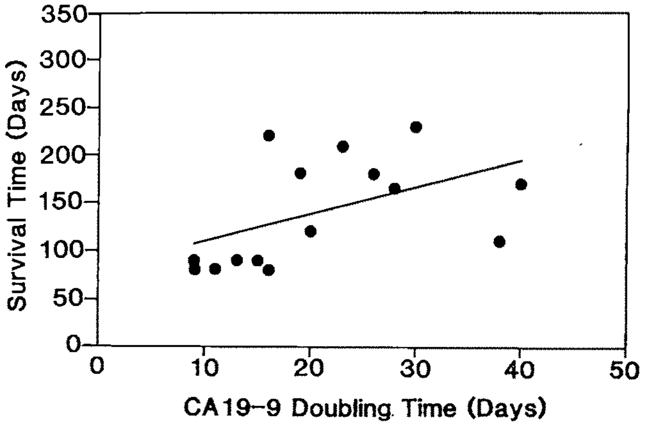

FIG. 6. The linear correlation between survival time and doubling time of serum CA 19-9 levels in 15 patients with marked increases of CA 19-9 levels before death ($r = 0.5$, $p < 0.05$).

Le^{a-b-} pancreatic cancer patients cannot express CA 19-9 because they do not have the oligosaccharide of the Lewis antigen to which sialic acid is added to form the CA 19-9 epitope. Approximately 5% of the population are Lewis type negative.[21] Consequently it is reasonable to reject Le^{a-b-} patients as candidates for serum CA 19-9 monitoring of their disease progression. In addition, poorly differentiated neoplasms may lack production of the CA 19-9 antigen.[22] In the current series, 4 of 38 patients belonged to the Le^{a-b-} group (11%). All CA 19-9 serum levels of these four patients, before and after operation, including their preterminal levels, were less than 61 U/mL. Excluding these four patients, the preoperative sensitivity of CA 19-9 assay improved, the median value rising from 330 to 360 U/mL.

Our data in the 34 Lewis positive patients indicate that higher levels of serum CA 19-9 are correlated with larger tumor sizes even though much overlap existed. This supports the concept that CA 19-9 levels can be used as an indicator of tumor burden. Also, relatively low CA 19-9 levels suggest a likelihood of resectability of the pancreatic cancer, because in 6 of 11 Lewis-positive resectable patients, the preoperative CA 19-9 levels were below 200 U/mL. Although only slightly elevated serum CA 19-9 levels can reflect a better prognosis for patients with pancreatic cancer, such values require that other diagnostic means be used to rule out nonmalignant pancreatic or biliary tract diseases.[2,16]

The comparison of the postoperative serum CA 19-9 levels with the preoperative level could, from our observation of 11 resectable Lewis-positive patients, provide information about the effectiveness of the operative resection. Each of the 11 patients who had their tumors removed had a sharp decrease in CA 19-9 serum concentration. Furthermore, the survival time in the seven patients in whom postoperative CA 19-9 dropped to the normal range was significantly longer than in the four with persistently elevated CA 19-9 levels. Each of the latter four patients died of tumor recurrence or distant metastasis that had become evident much earlier than in the group with normal postoperative CA 19-9 levels. This suggests that the persistently elevated serum CA 19-9 level reflects the presence of a "critical volume" of cancer. By comparison, simple laparotomy and biopsy, without resection, resulted in no significant change in the CA 19-9 levels in 11 patients without obstructive jaundice. Similarly, in nine patients with preoperative jaundice, biliary bypass resulted in only a slight decrease in CA 19-9 levels. Studies of the metabolic degradation of the CA 19-9 have not yet been reported in the literature. Serum CA 19-9 levels, however, decrease in the patients after biliary decompression, presumably as a result of improved hepatic function and biliary drainage rather than from any regression of the cancer per se.[7,23]

After the decrease of the CA 19-9 level after resection, a secondary rise is very suggestive that a clinically significant metastasis or local recurrence is evolving. Of 11 resectable patients, six who subsequently developed recurrence or metastasis had a secondary elevation in CA 19-9 before the CT scan or clinical evaluation demonstrated the lesions. Five of the six died of the cancer. The lead time of CA 19-9 assay was from 2 to 9 months. One individual in the group of 11 patients did not show a secondary elevation before death, even though he was verified as being Lewis positive.

A review of the literature[12,24,25] indicates that survival time after diagnosis, expressed in multiples of doubling time of various serum tumor markers, can be used as a basis for prognosis and for evaluating the effect of various therapeutic modalities. Effectively treated cancer patients may survive up to 20 or more doubling times, as opposed to ineffectively treated patients, whose life expectancy may be only a few doubling times.[12] In our patients, the rate of the increase of CA 19-9 concentration could, to some extent, be correlated with the survival time both in resectable and in unresectable patients. The survival time ranged from 2.9 to 13.8 times the doubling time. Because many factors in clinical practice influence the survival time, an exact correlation could not be expected. In 23 patients, however, who died of their cancer, 15 (65%) revealed an increasing CA 19-9 level before death. A linear correlation between doubling time and survival time was found This suggests that any therapeutic procedure that slows the rate of serum CA 19-9 increase should prove effective in prolonging the survival of patients with pancreatic carcinomas.

From our data, we conclude that the serum CA 19-9 assay is useful for monitoring the progress of the disease in patients with either resectable or unresectable pancreatic adenocarcinomas. Serial examination of serum levels of this antigen in the Lewis-positive patient apparently reflects the tumor burden at any given time. Hopefully, as with the carcinoembryonic antigen level in the patient with cancer of the colon, a secondary rise in the CA 19-9 level may alert the physician to the need for careful re-evaluation of his patient's therapy.

Conclusions

Among 34 patients who were Lewis blood type positive, significantly lower serum CA 19-9 levels were found preoperatively in those patients with the smaller cancers and in those whose cancer proved resectable. After resection of the tumor, the serum concentration of CA 19-9 decreased. A secondary rise in the serum level preceded, by 2 to 9 months, the verification of recurrence or metastasis by other means. Among those patients whose CA 19-9 level decreased to the normal range after resection, the subsequent survival time was significantly longer than was the survival time of those patients whose CA 19-9 level remained higher than normal after resection. In the overall group, 23 of 34 Lewis-positive patients who died during the course of the study, 65% of the patients demonstrated an obvious rise in CA 19-9 level before death. Among the four patients (11%) who were Lewis blood type negative, none showed a significantly elevated CA 19-9 level during the course of their disease. Thus, in 89% of the patients who are Lewis blood type positive, the CA 19-9 serum antigen level provides a useful indicator of the prognosis and effectiveness of the treatment of cancer of the exocrine pancreas.

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Cytokine Serum Level During Severe Sepsis in Human IL-6 as a Marker of Severity

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Forty critically ill surgical patients with documented infections were studied during their stay in an intensive care unit. Among these patients, 19 developed septic shock and 16 died, 9 of them from septic shock. Interleukin 1β (IL-1β), tumor necrosis factor (TNFα), and interleukin 6 (IL-6) were measured each day and every 1 or 2 hours when septic shock occurred. Although IL-1β was never found, TNFα was most often observed in the serum at a level under 100 pg/mL except during septic shock. During these acute episodes TNFα level reached several hundred pg/mL, but only for a few hours. In contrast, IL-6 was always increased in the serum of acutely ill patients (peak to 500,000 pg/mL). There was a direct correlation between IL-6 peak serum level and TNFα peak serum level during septic shock and between IL-6 serum level and temperature or C-reactive protein serum level. Moreover, IL-6 correlated well with APACHE II score, and the mortality rate increased significantly in the group of patients who presented with IL-6 serum level above 1000 pg/mL. Thus, IL-6 appears to be a good marker of severity during bacterial infection.

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INTERLEUKIN 1β (IL-1β) AND TUMOR NECROSIS FACTOR α (TNFα) are two cytokines primarily produced by activated macrophages in response to injury.[1] They mediate several systemic changes associated with trauma or infection such as fever, neutrophilia, and increased hepatic acute phase protein synthesis.[2] It is now thought that many of the consequences of bacterial sepsis are due to the release of these polypeptides. In particular, TNFα has been shown to be involved in septic shock.[3] When injected intravenously in animals, it produces the same effects as endotoxin[4,5]; passive immunization against TNFα also protects mice, rabbits, or baboons from the lethal effects of endotoxin or gram-negative bacteremia.[6-8] In humans, TNFα can be detected in the serum of volunteers after endotoxin injection.[9,10] During septic shock, high TNFα serum levels have been observed by many authors in severely ill pediatric or adult patients.[11-16] The role of IL-1β is less clear; like TNFα it can induced a shock state in rabbits,[17] and high peak levels were observed in purpura fulminans by Girardin et al.[12]

Interleukin 6 (IL-6) is another cytokine that appears to be the most efficient stimulator of the production by the liver of the acute phase proteins. It is probably a second messenger released by macrophages, endothelial cells, or fibroblast and other cells in response to IL-1β or TNFα.[18] High serum levels of IL-6 measured by bioassay have already been found during sepsis in humans.[19,20]

To document the involvement of IL-1β, TNFα, IL-6 in human infection, and in particular in septic shock, we investigated critically ill patients during the course of bacterial infections.

Materials and Methods

Patients

Forty critically ill patients with documented infections were studied during their stay in a surgical intensive care unit. All patients (or their relatives) gave us informed consent to draw blood and perform cytokines measurement. There were 20 intra-abdominal infections (12 with gram-negative bacteria [GNB], 2 gram-positive cocci, 2 anaerobic bacteria, and 4 with mixed flora), 5 mediastinitis (1 *Staphylococcus aureus*, 4 GNB), 3 bronchopneumonia (1 *S. aureus*, 2 GNB), 9 septicemia (1 *S. aureus*, 8 GNB), 2 vascular graft infections (1 *S. aureus*, 1 GNB) and 1 post-traumatic meningitis (1 GNB). For these patients, the usual clinical and biologic parameters, temperature, and leukocytosis were measured each day; serum C-re-

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active protein (CRP) was measured once a day, 5 days per week. APACHE II score, which is based on 12 bioclinical parameters in addition to age and chronic organ system failure, was recorded for each patient every day.[21]

During the course of infection, the diagnosis of septic shock was defined according to the following criteria: (1) systolic blood pressure less than 90 mmHg for more than 1 hour, or a fall of 50 mmHg in a previously hypertensive patient, (2) a rise in temperature to more than 39 C or a fall to less than 35 C, (3) a lactatemia equal or superior to 2.5 mmoles/L or oliguria of less than 20 mL/hour for 5 hours.

Sampling

Blood was drawn by venipuncture or using an indwelling arterial catheter into sterilized siliconed glass tubes (Becton Dickinson, Meylan-Cedex, France). The 40 patients were sampled once a day at 8:00 A.M. during 11.3 ± 9.7 days (range, 1 to 35); in addition, 20 of these patients were sampled 3.6 ± 1.8 times a day (2 to 8), every 1 or 2 hours as soon as they presented a septic shock state; septic shock was confirmed in 16 of these patients. Three other patients presented a septic shock during which only one sample was drawn. Clotting was obtained at room temperature. Blood samples then were centrifuged at 3000 rpm for 10 minutes, and separated serum was stored at −20 C until use.

Interleukin-6 was measured by a two-step immunoradiometric assay (IRMA) from Medgenix (Belgium). Briefly, the two-step IRMA is based on coated tube separation and on an oligoclonal system in which several monoclonal antibodies are directed against distinct epitopes of IL-6. The capture antibodies are attached to the lower and inner surface of plastic tubes. Two hundred microliters standard control solution and an equal volume of serum samples are each placed into duplicate coated tubes together with 50 μL of a special diluent. The tubes then are incubated for 16 to 20 hours at room temperature. The complete content is then aspirated and the tubes washed with Tween 20 (Merck, München, Germany) in distilled water (5%). After this procedure, 200 μL tracer, which is another monoclonal antibody labeled with I^{-125}, is added to the tubes for 2 hours. The tubes then are washed again and are counted in a gamma counter for 60 seconds. The IL-6 concentration of samples was determined by interpolation using a standard curve prepared at the same time. Interleukin-1β and TNFα were measured by a one-step IRMA using available kits from Medgenix (Belgium). The procedure of the one-step IRMA is the same as for the two-step IRMA, except that the standards or samples are incubated together with 50 μL tracer. The sensitivity of these IRMA assays are 5 pg/mL for TNFα and IL-6 and 4 pg/mL for IL-1β. In normal subjects, no IL-1β, no TNFα, and no IL-6 could be detected by IRMA.

C-reactive protein serum level was measured by nephelometry.

Statistics

Comparisons of biologic parameters or clinical scores between groups of patients were made using Student's test. To normalize the distribution of IL-6 and TNFα serum results, and to permit the use of the t test, we used the log of the serum level, which is comparable to the median. The relationships between biologic or clinical parameters were tested by linear regression using standard formulas and chi square was used to establish a correlation between IL-6 serum level and mortality rate. The level of significance was fixed at 5%.

Results

Among the studied patients, there were 29 men and 11 women, with a mean age of 60.5 ± 12.6 years (range, 29 to 82). The severity of their illness was assessed by APACHE II score, which, as a mean, was 21.4 ± 6.7 at day 1. The mean time of their stay in the intensive care unit (ICU) was 24 ± 6.7 days. Nineteen patients developed septic shock as defined above, and 16 patients died, 9 of them from septic shock. Shock was due to GNB in 16 cases, to *S. aureus* in 3. As shown in Table 1, APACHE II score at day 3 was statistically different between survivors and nonsurvivors, but it could not distinguish between patients with or without septic shock.

Interleukin-1β was never found in the serum of any patient, even if they were sampled hourly during a septic shock episode. Tumor necrosis factor-α serum levels were just above the detectable level in most patients. In patients without septic shock ($n = 21$), only 52% of the samples contained TNFα. In five of these patients, TNFα was never found, whereas six patients only showed serum levels above 100 pg/mL; the maximum observed, in a patient with peritonitis, was 255 pg/mL (Fig. 1C). In the four patients without septic shock who were sampled 4 times in a day, TNFα serum levels remained low and constant. Conversely, patients with septic shock ($n = 19$) showed a brief TNFα peak during the acute episode, with a rapid return to lower values as shown in Figure 1A and B. The mean peak value of TNFα during septic shock was 735.9 ± 873 pg/mL (range, 10 to 3348), whereas it was 67.1 ± 63.7 pg/mL in patients without septic shock ($p < 0.001$). Three of the nineteen patients with septic shock did not have high levels of TNFα in their serum (*i.e.*, <100 pg/mL); they were all sampled the day after the onset of shock. Figure 2 shows the negative correlation between the peaks of TNFα serum level and leukocyte count measured at the same time in each patient ($r = -0.54$, $p < 0.01$). The time during which TNFα could be found in the serum did not differ between survivors and nonsurvivors.

TABLE 1. *Cytokine Peak Serum Levels in Patients According to the Presence of Shock or the Occurrence of Death*

	Survivors	Nonsurvivors	Without Shock	With Shock
No. of patients	24	16	21	19
Age	58.3 ± 13.2	63.7 ± 11.6	60.8 ± 12.7	59.8 ± 13.5
APACHE II				
Day 1	20.2 ± 6.1	23.2 ± 7.3	19.9 ± 6.6	22.8 ± 6.7
Day 3	13.6 ± 4.6*	23.7 ± 6.5*	16.4 ± 6.3	18.5 ± 8.4
IL-1β peak serum level	0	0	0	0
TNF peak serum level (pg/mL)				
Median	93	120	57*	471*
Range	25–2286	10–3448	25–255	10–3348
IL-6 peak serum level (pg/mL)				
Median	1434	6598	788*	10049*
Range	200–217774	180–461850	180–3868	200–461850

* $p < 0.05$.

In contrast to IL-1β and TNFα, IL-6 serum levels were almost always above normal value during bacterial infection (Fig. 3). Only one patient was observed to have a normal value at the end of his stay in the ICU. Most values were between 10 and 1000 pg/mL, with some extreme levels reaching 500,000 pg/mL. The serum level of IL-6 seemed to be correlated with the severity of the illness. As shown in Table 1, there was a large difference between IL-6 peak levels observed in survivors and in nonsurvivors, as well as between patients with and without septic shock. Because of the high standard deviation, however, only the difference between septic shock and nonseptic shock was statistically significant. Furthermore, a good correlation could be observed between the log of IL-6 serum level and the APACHE II score obtained the day of the IL-6 peak as well as on day 3 or day 7 (Fig. 4). Several parameters also were found to be correlated with IL-6 serum levels: temperature, as shown by Figure 5, and CRP by Figure 6. This last figure was made taking the highest levels of IL-6 and the CRP serum level obtained on the

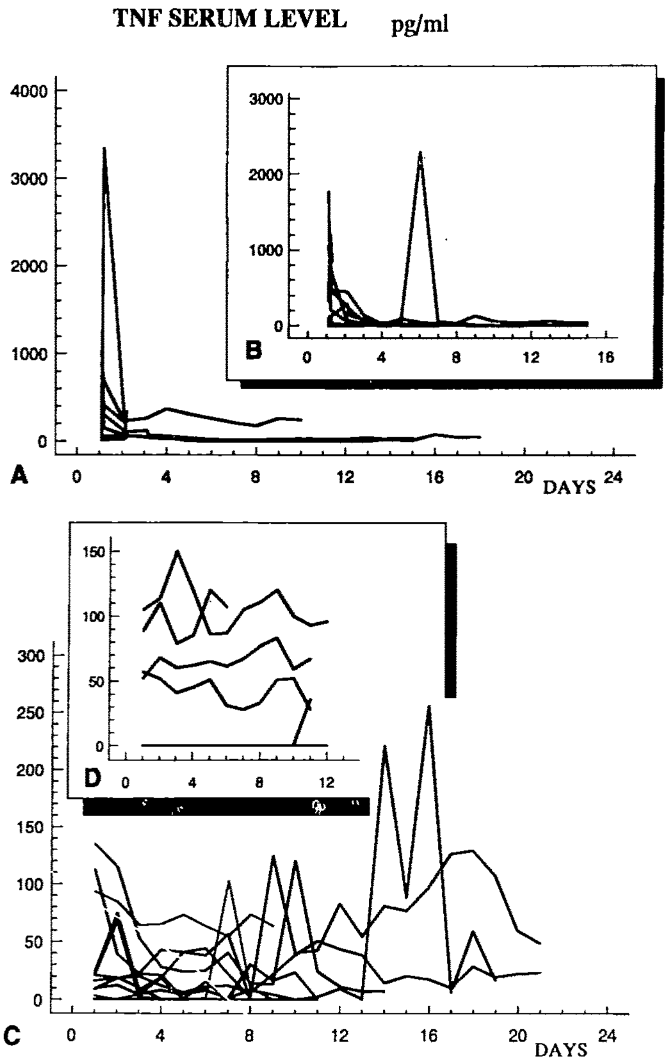

FIG. 1. Time course of TNFα serum levels during infection in patients with (A, nonsurvivors; B, survivors) and without septic shock (C, survivors; D, nonsurvivors).

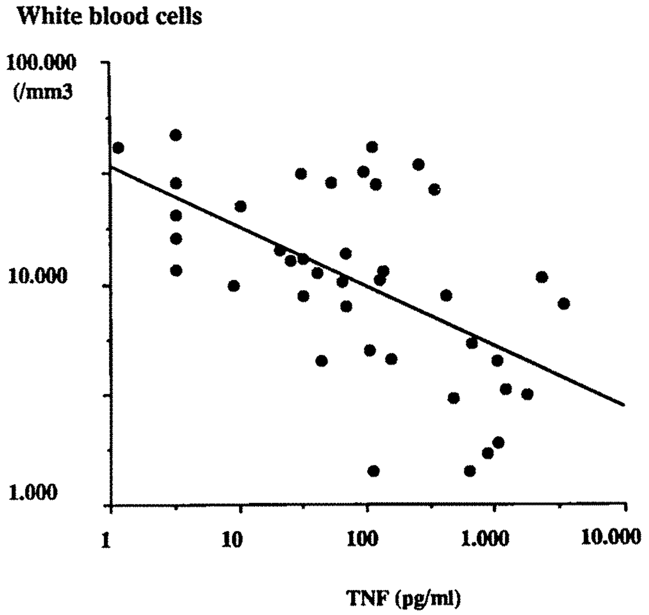

FIG. 2. Relationship between peak serum level of TNFα and white blood cell count measured at the same time ($r = -0.57$, $p < 0.001$).

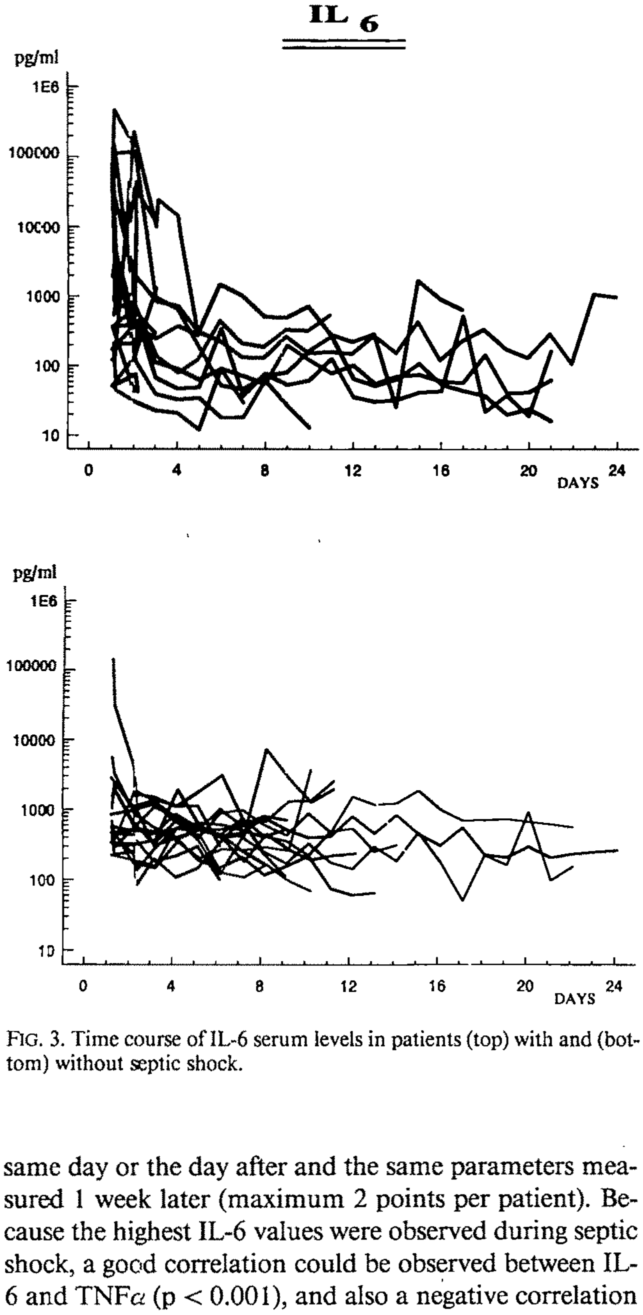

FIG. 3. Time course of IL-6 serum levels in patients (top) with and (bottom) without septic shock.

same day or the day after and the same parameters measured 1 week later (maximum 2 points per patient). Because the highest IL-6 values were observed during septic shock, a good correlation could be observed between IL-6 and TNFα ($p < 0.001$), and also a negative correlation between IL-6 and leukocytosis ($p < 0.001$). No correlation could be found, however, between IL-6 and lactate level or platelet count.

Discussion

Interleukin-1β could not be observed in our patients even at the time of septic shock. Several authors, however, have reported high serum or plasma levels of IL-1β during sepsis in animals or humans, using bioassay, radioimmunoassay, or enzyme-linked immunoassay.[12-15,19] The specificity of these assays may be questioned because some bioassays also may have been sensitive to IL-6,[22] and some immunoassays detected significant levels of IL-1β in healthy volunteers. Hesse et al.[9] described an increase in serum level of IL1β after the peak of TNFα, using a bioassay in normal volunteers challenged with endotoxin IV, whereas Michie et al.[10] did not observe any change in IL-1β measured by immunoassay. The high recovery of IL-1β added to either normal plasma or serum from septic patients suggests that the presence of serum inhibitors of IL-1β could not have impaired the detection of IL-1β in our patients. The involvement of circulating IL-1β during severe infection thus remained a matter of debate. Some recent studies, however, showing the protection by a receptor antagonist for IL-1 in septic shock model in animals support the role of IL-1.[23,24]

Tumor necrosis factor alpha is thought to be an early mediator of septic shock and has already been found by many authors in the serum of patients in septic shock. No longitudinal studies have yet been reported, however, except after burn injury.[25] This study confirms the involvement of TNFα in septic shock; high peak levels were observed in almost every episode of septic shock, and only during this acute event. Three patients were sampled too late after the onset of septic shock, and their TNFα serum levels were low, confirming the negative correlation between the peak serum level of TNFα and the time elapsed from the onset of shock already observed in a previous study.[13] In patients without shock or in the other patients beyond the septic shock episode, TNFα serum levels usually remained under 100 pg/mL. There was no correlation between the time during which TNFα could be found in the plasma and death. These data are consistent with those reported after endotoxin challenge in human volunteers, where a brief increase of TNFα serum level, negatively correlated with leukocyte count,[10] also was seen. This may be due to IL-8, however, another cytokine released after

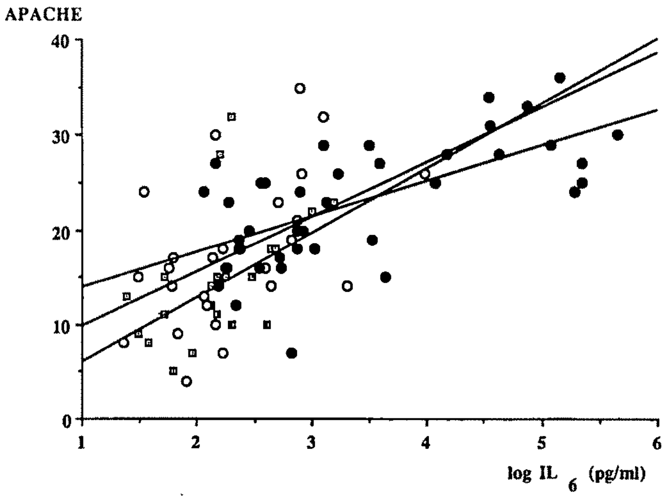

FIG. 4. Relationship between IL-6 serum level and APACHE II score. ●, peak value of IL-6; ○, IL-6 serum level at day 3; ☐, IL-6 serum level at day 7 ($r = 0.63$, $p < 0.001$).

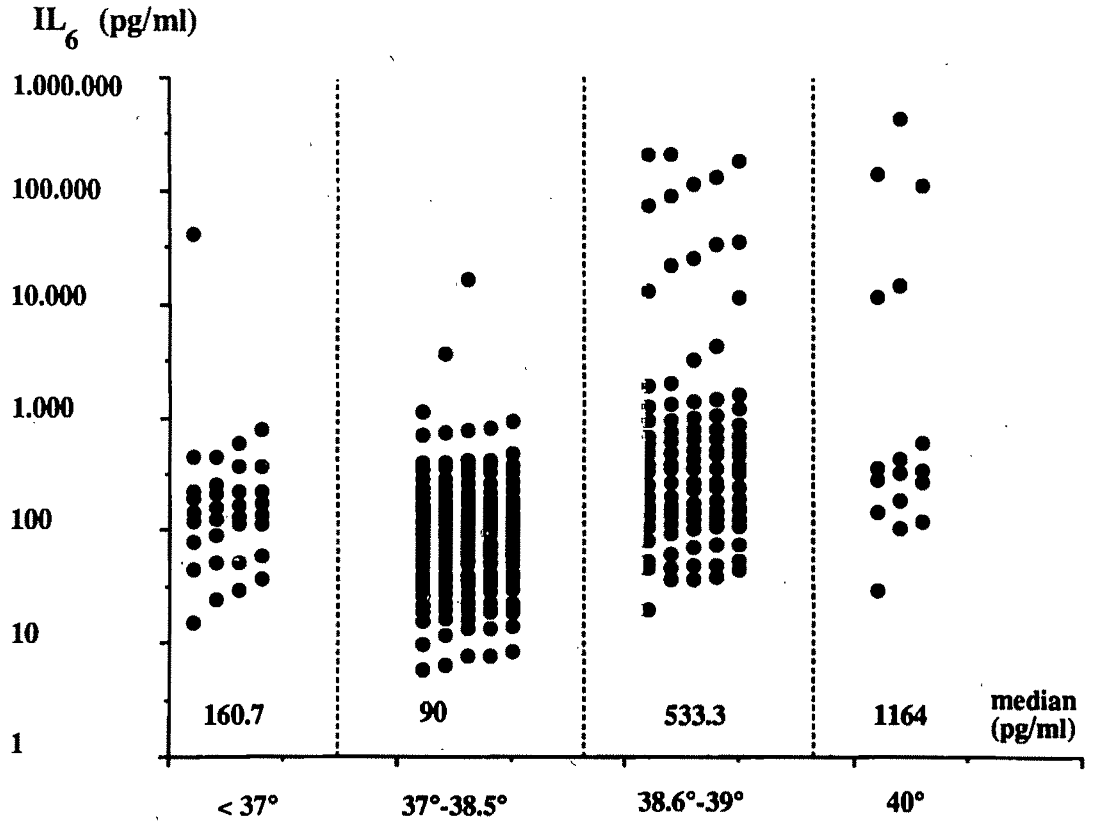

FIG. 5. Correlation of IL-6 serum level with maximum recorded temperature on the same day for the entire group of 40 patients. Median is the mean of the log of IL-6 serum level. The differences between these mean values are highly significant ($p < 0.001$).

TNF and IL-1 in the cytokine cascade.[26] During infection, when the leukocyte count was very high, we never observed high levels of TNFα.

The brief increase in TNFα serum level does not allow us to use this level as a prognostic threshold. As shown in Table 1, the prognosis depends on the APACHE II score rather than on a transient serum level, which can be missed.

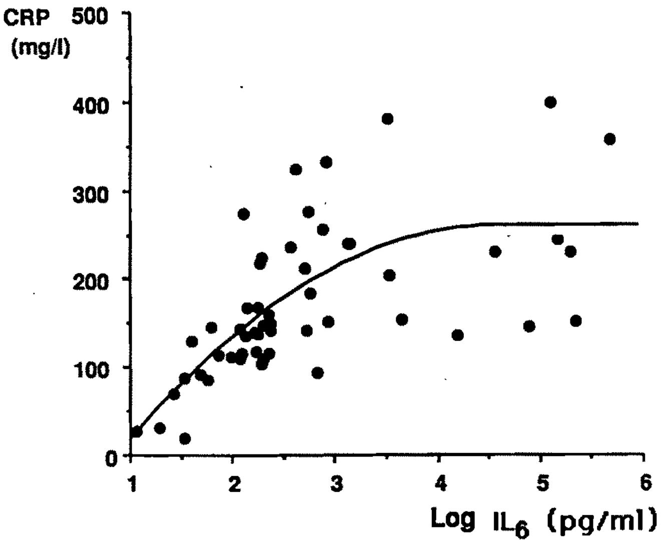

FIG. 6. Relationship of IL-6 and CRP serum levels (CRP measured within 24 hr of IL-6) on the day of peak IL-6 and 1 week later ($r = 0.66$, $p < 0.001$).

After IL-1β and TNFα, IL-6 is the third cytokine described to be involved in the acute phase response. Its multiple effects contribute to a coordinated response of the body to aggression: it acts to render T cells and hematopoietic cells responsive to their respective growth and differentiation factors, it initiates acute phase protein synthesis in the liver, and stimulates antibody production.[18] Its presence in the serum or plasma has already been reported in several circumstances, including burn injury,[27] after surgery,[28] during acute graft rejection,[29] in myeloma,[30] or during sepsis.[19,20] High plasma levels of IL-6, exceeding 10,000 pg/mL, have only been observed in septic patients using a bioassay.[20] After endotoxin injection in volunteers, a peak IL-6 plasma level of 25 ng/mL was observed after 2 to 4 hours, followed by a peak of CRP at 20 hours.[31] During acute graft rejection or after surgery, IL-6 levels were much lower, in the range of 100 to 1000 pg/mL.[29,30]

Our results confirm those of Hack et al.,[20] who found levels up to 150,000 pg/mL in septic patients at the time of admission to the ICU. Rather than the direct correlation with mortality rate described by Hack et al., however, we found a significant correlation between the high serum levels of IL-6 and the illness severity as assessed by the APACHE II score. We found a level of 1000 pg/mL, above which the mortality rate significantly increased from 21% to more than 50%; this percentage did not change in patients demonstrating IL-6 levels higher than 100,000 pg/mL. The same can be seen with the APACHE II score, which could not differentiate between survivors and nonsurvivors on admission to the ICU. Thus, the outcome of patients does not depend on one measure only; it is rather the failure to respond to treatment, as shown by the APACHE II score on day 3, which is the valid predictor. The fact that IL-6 is really a marker of severity is emphasized by the correlation with APACHE II score which still exists at day 3 and day 7. One could say, however, that the APACHE II score is validated by such a correlation. As can be seen in Figure 4, however, several particular APACHE II scores were still high in spite of the decrease of their respective IL-6 levels, indicating that IL-6 seemed to return to baseline more rapidly than the correction of the clinical status as already mentioned by Hack et al.

Because IL-6 serum levels were very high during septic shock, it is not surprising to find a correlation between peak IL-6 and TNFα serum levels, as well as a negative correlation between peak IL-6 serum levels and leukocytosis. Tumor necrosis factor alpha peaks and the relative leukopenia were transitory events: therefore, this relationship appears to be ephemeral and is no longer evident after septic shock. More interesting is the relation between IL-6 and temperature, and especially CRP. Interleukin-6 is considered to be an endogenous pyrogen, and its serum level has been shown to be directly related to temperature after burn injury.[23] In this study, there was a considerable overlap of IL-6 serum levels between the different temperature intervals; the distribution, however, showed a statistically significant progressive increase of IL-6 as a function of recorded temperature. The relation to CRP, however, may be questioned because it was obtained using the peak serum level of IL-6 and the CRP serum level observed within 24 hours after this peak, as well as the same levels measured 1 week later in the same patients, when both decreased. It would have been preferable to document this relationship using different degrees of severity of infection and not the recovery phase after infection. This can be compared, however, with the results obtained after surgery: a direct relationship between the log of IL-6 serum level at 24 hours after surgery, and the peak of CRP serum level at 48 hours could be observed.[32] The plateau obtained for the response of CRP to very high levels of IL-6 with a relative dispersion of the results as shown in Figure 6 may be due to the fact that these points were obtained in severely ill patients with multiple system failure; thus, liver function and hepatic responsiveness to IL-6 may have been impaired. The involvement of IL-6 in the pathophysiology of sepsis and septic shock may be questioned in view of the relationship between serum level of IL-6 and the severity of the disease; it appears from animal studies, however, that this cytokine functions as an alarm signal, leading to the recruitment of host defenses.[18] This study emphasizes the high magnitude of this signal.

In conclusion, although IL-1β could not be found in the serum of infected patients, TNFα was observed mainly as a brief pulse at the time of septic shock. Interleukin-6 was, in contrast, often found at a serum level correlated to the severity of the illness, as assessed by APACHE II score, and to the acute phase response, as shown by its relationship with temperature and CRP.

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Delayed Gastric Emptying After Roux-en-Y due to Four Types of Partial Obstruction

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Partial obstruction was the cause of delayed gastric emptying in 12 patients after a Roux-en-Y gastrojejunostomy in a consecutive personal series of 42 patients between 1975 and 1989. Four types of obstruction were identified. Type I was due to a kinked loop of jejunum where it passed through the mesocolon. Type II had the anastomosis too high on the gastric pouch, type III was due to an obstructing marginal ulcer, and type IV had a pouchlike deformity develop in the upper jejunum at the anastomosis that gradually compressed the outflow tract. No patient had stenosis of the anastomosis. The upper gastrointestinal (GI) series plus nuclear studies of the liquid and solid phase gastric emptying provided evidence of the presence and degree of delayed gastric emptying but not the site or cause of the obstruction. Upper GI endoscopy provided precise evidence of the site of the partial obstruction, its anatomic nature, and the presence of a bezoar or marginal ulcer. Of the 42 patients, 4 had surgical correction, and in 6 patients the obstruction was relieved by endoscopic manipulation; all patients have been relieved of their symptoms. Partial obstruction was the only cause of delayed gastric emptying in this series, and contrary to recent reports, no patient required a total or near total gastrectomy.

THE ROUX-EN-Y GASTROJEJUNOSTOMY has been shown to be the most effective method of treating enterogastric reflux gastritis.[1] This type of gastritis has been found after all gastric procedures that destroy or bypass the pyloric sphincter, and it also occurs spontaneously, especially in patients after cholecystectomy (Fig. 1).[1,2] Sawyers et al.[3] have compared the Roux-en-Y anastomosis with the Tanner-19 and the jejunal interposition and have found the results of the Roux-en-Y procedure to be superior.[3] Drapanas and Morrison[4] observed that if the Roux-en-Y anastomosis is the best way to correct enterogastric reflux, then it should be used to avoid it.[4] With increasing frequency, vagotomy, antrectomy, and Roux-en-Y gastrojejunostomy has been the operation of choice when gastric resection was indicated.[2-8]

The most frequently encountered problem after Roux-en-Y gastrojejunostomy is delayed gastric emptying, which occurs in 25% to 30% of cases.[9-12] Some authors have attributed the delay to failure of the fundus to contract in a forward coordinated peristaltic fashion.[12-15] The most that can be said for the motor function of the fundus is that it has tone but not peristalsis. Attempts to induce peristaltic activity in the gastric pouch using pharmacologic agents have failed, for example, metoclopramide, bethanechol, domperidone and cisapride. In more than 1000 upper gastrointestinal (UGI) endoscopies, I have never observed peristalsis in the fundus, and this includes the intact stomach as well as post-Billroth II hemigastrectomy with end-to-side anastomosis or the Roux-en-Y anastomosis. After a hemigastrectomy or subtotal gastrectomy, with or without vagotomy, the fundus empties by gravity.

A second approach to the problem of delayed gastric emptying has been to study the peristaltic activity of the jejunum. Simply dividing and anastomosing the jejunum will create disorganized peristalsis, and coordinated function is temporarily interrupted. Motor function of the jejunal limb has been studied by Miedema and Kelly,[16] and the possible need for a pacemaker has been studied but not found useful.[16] Mathias et al.[17] has shown similar findings in a small series. The problem of disorganized peristalsis must be temporary because it resolves completely without specific therapy in most patients. In addition, most authors find that 70% of their patients do well after the Roux-en-Y procedures, so that disorganized peristalsis is neither a constant nor a predictable finding. Pellegrini et al.[9-11] have pointed out that there is no consistent pattern of gastric emptying in patients with reflux gastritis, and there is no consistent effect of the Roux-en-Y reconstruction.[9-11] Furthermore, in some patients,

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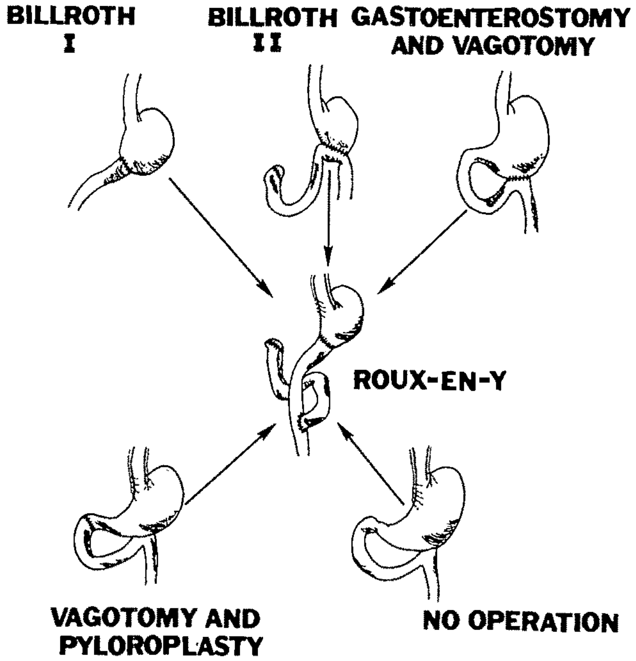

FIG. 1. Enterogastric reflux gastritis can occur after all operations that either bypass or destroy the pyloric sphincter; It can also occur spontaneously.

symptoms suggestive of delayed gastric emptying were unrelated to the emptying of a solid-phase "hot-meal"; in fact, in some patients there was rapid emptying in these radionuclide studies.

A third possible cause of delayed gastric emptying is partial obstruction at or near the anastomosis, but not stomal stenosis per se. Forty-two patients in a consecutive personal series, from 1975 to 1989, had Roux-en-Y gastrojejunostomy and 12 developed delayed gastric emptying. Four types of outflow obstruction have been identified and are the subject of this report.

Materials and Methods

Between 1975 and 1989, in a consecutive personal series, 42 patients had Roux-en-Y gastrojejunostomy of 40 to 60 cm. Two patients died in the early postoperative period, one of heart failure 10 days after Whipple resection for carcinoma, and one of necrotizing pancreatitis after gastrectomy for duodenal ulcer. Forty patients remain for evaluation.

The indications for Roux-en-Y anastomosis were benign peptic ulcer in 15, enterogastric reflux in 18, carcinoma of the stomach in 4, Whipple resection in 2, congenital duodenal obstruction in 1, gunshot wound of duodenal bulb in 1, and marginal ulcer in 1 (Table 1).

All patients had nasogastric suction until peristalsis was noted, the abdomen was flat, and flatus had been passed. At this point, the nasogastric tube was removed and clear noncarbonated liquids were started on an hourly basis and advanced to nourishing liquids and then progressively to anti-dumping diet. Patients with early satiety, nausea, and vomiting were studied with UGI series and UGI endoscopy, and more recently two patients had radionuclide gastric emptying studies. This study was not available in the early stage of this series.

Results

Twelve of the forty patients developed delayed gastric emptying due to partial obstruction; one patient had type I early and 3 years later type IV. There were 18 men and 24 women. The age range in men was 33 to 74 years, with a median age of 60. The age range for women was 25 to 82 years, with a median age of 57. Thirty-two of the forty-two operations were performed between 1975 and 1982, and of these, 17 were performed between 1975 and 1977. Follow-up ranged from 1 to 12 years, averaging 5 years (Fig. 2).

Four types of partial obstruction were identified (Fig. 3). Types I and II were found immediately as feeding was started, whereas types III and IV developed 1 to 6 years after operation.

Type I was due to a kinked loop of jejunum 10 to 15 cm below the anastomosis, where the jejunum passed through the transverse mesocolon. The UGI series was misinterpreted as anastomotic obstruction, but by UGI endoscopy, the anastomosis was observed to be widely patent. The jejunum was normal for 10 to 15 cm, became narrowed for 2 to 3 cm, and was again normal in caliber. The gastroscope was then withdrawn until the tip of the scope engaged the narrowed segment, and it then was possible to manipulate the tip in four directions, and thus to stretch or release recently formed adhesions. This technique has been the subject of a previous report.[8] It was necessary to repeat this endoscopic manipulation in two of six patients. All patients were relieved of their obstruction and were able to tolerate an anti-dumping diet. None of these patients required surgical intervention in 5 to 12 years' follow-up.

TABLE 1. *Indications for Roux-En-Y Anastomosis*

Indication	No.
Peptic ulcer–vagotomy antrectomy	15
Enterogastric reflux gastritis	18
Carcinoma of stomach	4
Whipple resection for carcinoma	2
Duodenal obstruction, malrotation	1
Trauma–GSW duodenal bulb	1
Marginal ulcer	1
	42

GSW, gunshot wound.

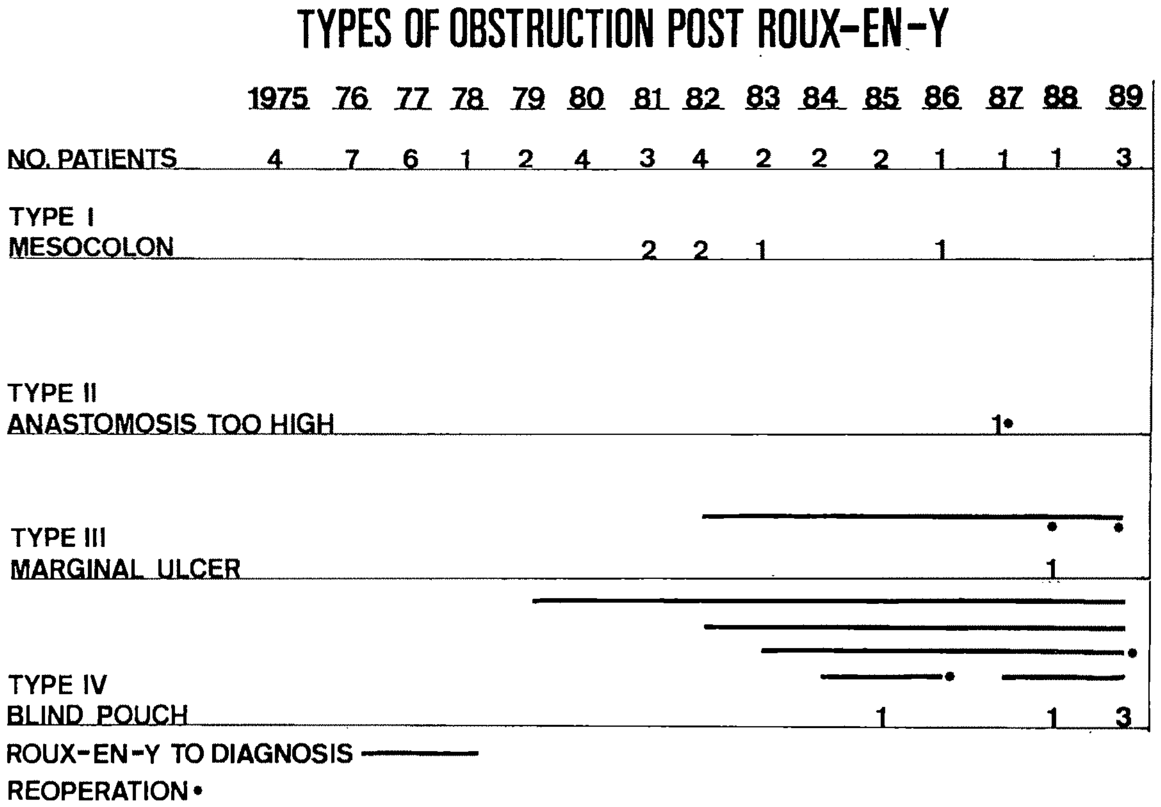

FIG. 2. Timing of operations shows that type I obstruction clustered between 1981 and 1983, but none occurred in the previous 6 years. The patient with type III obstruction and the marginal ulcer required two procedures. In the patients with type IV obstruction, the jejunal pouch deformity gradually developed over 2 years in two patients, but it took 6, 7, and 10 years to develop in others.

Type II

The anastomosis is placed too high on the gastric fundus, thus creating a dependent sac that cannot empty by gravity. This problem was noted in one patient who had early satiety, nausea, and vomiting. The UGI series showed delayed gastric emptying, and the anastomosis was shown to be too high. Upper GI endoscopy demonstrated the anastomosis to be patent but too high for effective drainage. This problem was corrected by performing a new gastrojejunostomy, side to end, in a more dependent position, and the patient then was able to tolerate a normal diet. The patient remains well at 4 years.

Type III

Marginal ulcer was observed in three patients but proved to be obstructive in only one patient who had a "giant marginal ulcer." This patient had a truncal vagotomy and Billroth II gastrojejunostomy in 1981, a conversion to Roux-en-Y-30 cm in 1983 for enterogastric reflux followed by cholecystectomy, then a laparotomy with lysis of adhesions before referral. She had constant nausea and progressed to vomiting after every meal with constant epigastric pain and a 15-lb. weight loss. The UGI series showed delayed gastric emptying but failed to identify a large bezoar and a large marginal ulcer. Upper GI endoscopy demonstrated the bezoar and, once removed, a marginal ulcer was found that was not only circumferential but extended down the jejunum for 8 cm. Bile was present in the gastric pouch. The pathologist at the previous hospital had identified two vagal trunks; serum gastrins were normal, secretin test was normal, technetiun scan did not show an antral remnant, serum calcium was normal, and gastric analysis showed low basal and maximal acid outputs. At operation, the site of the marginal ulcer was noted to be firm and fibrous. This segment was resected and a new gastrojejunostomy was performed. The Roux-en-Y 30 cm was converted to a Roux-en-Y-60 cm. The marginal ulcer and bezoar formation recurred in 9 to 12 months, so a transthoracic vagotomy plus resection of the upper jejunum and a new gastrojejunostomy were performed. At 6 months and 1 year, repeat UGI endoscopy remained normal, the Congo Red Test at 6 months postoperatively was normal, and the patient remains well at 3 years, can tolerate a normal diet, and has regained her weight.

Type IV obstruction is due to the gradual development of a jejunal pouch and is due to three different mechanisms.

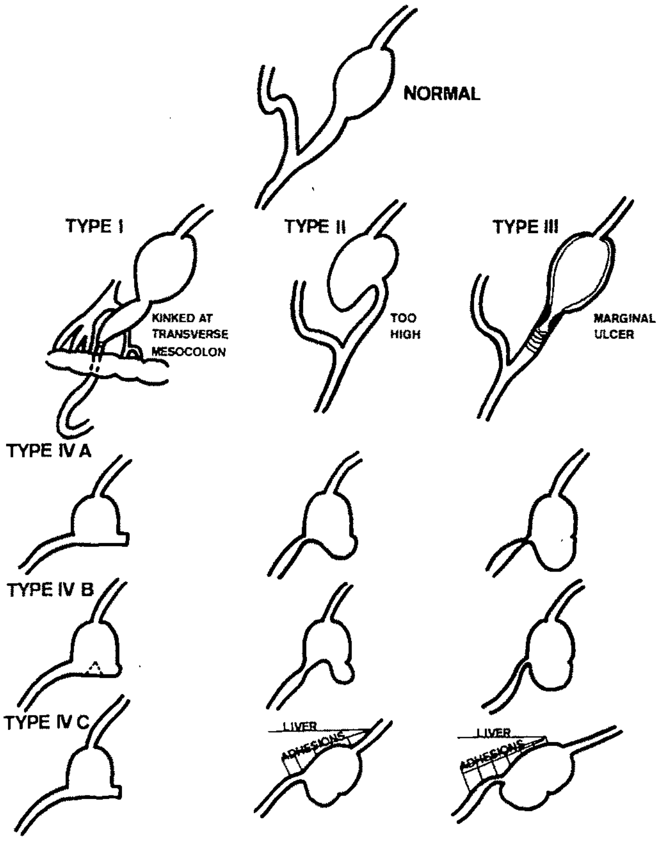

FIG. 3. Types I, II, and III are shown on the top row. Type IV A shows an initial overhanging pouch that gradually enlarges and displaces the outflow tract. In type IV B, the mesenteric wall can tent up into the anastomosis and produce a similar deformity to type II A. In type IV C, adhesions can cause severe angulation, yielding the same type deformity as in type IV A.

In the first, type IV-A, there is an overhanging pouch that slowly increases in size and eventually becomes so large that it fills preferentially from the gastric fundus. As the pouch increases in size, it compromises the outflow tract and the patients complain of constant epigastric fullness that is worse after meals. The UGI series can demonstrate the presence of the pouch and can document its progression. The UGI endoscopy, however, allows a more precise definition of the anatomic relationship of the gastric fundus, the anastomosis, the pouch, and the outflow tract. It also allows removal of the bezoar that is usually present.

Type IV-B occurs when there is a Polya type anastomosis with a long jejunal segment. If the mesenteric wall of the jejunal segment tents upward into the anastomosis, the stomach will drain on both sides of this median bar. This anatomic deformity sets the stage for a pouch to form that eventually increases in size and compromises the outflow tract in the same way as in Type IV-A. A similar process has been observed after a Billroth II end-to-side gastrojejunostomy, and when the tented up bar of jejunum reaches the anastomosis then all of the bile and pancreatic secretions in the afferent limb must enter the gastric pouch before they can drain into the outflow tract.

In Type IV-C, postoperative adhesions can form between the anastomosis and the liver or abdominal wall so that the anastomosis becomes angulated and a pouch is formed that results in the same process as in IV-A and B above.

It may take 1 to 10 years to develop, but each type IV process is associated with the slow onset of obstructive symptoms and similar radiographic and endoscopic findings. When the outflow tract becomes severely compromised, the patient will have constant fullness, vomiting after every meal, and weight loss. At this point correction with a new end-to-end anastomosis in a dependent position is the treatment of choice.

Discussion

The Roux-en-Y gastrojejunostomy has achieved its purpose in both correcting and avoiding enterogastric reflux gastritis. The gastric pouch empties by gravity, and if the anastomosis is patent, is placed in a dependent position, and there is no jejunal angulation, obstructing adhesions, or overhanging pouches, there should be normal drainage. Ferguson et al.[18] have recently reported their experience with the Roux-en-Y anastomosis, and delay was due to a pouch deformity of the jejunal limb if it was placed in an isoperistaltic position, whereas it did not occur if the tip of the jejunal limb was placed at the lesser curvature or anti-peristaltic position. Seventy per cent of the patients with the Roux-en-Y anastomosis do well, but delayed gastric emptying continues to be the most frequent problem. Efforts to induce peristalsis in the gastric pouch have failed, as might be expected because peristalsis was never a function of the fundus either in the intact stomach or in the postoperative gastric pouch. Some investigators have described disorganized or absent peristalsis in the divided jejunum as the cause of delayed gastric emptying.[12,13,15,17] If this is the prime problem, why is delayed emptying observed in only one third of these patients? Furthermore, if the delay is due to a motor disorder of the jejunum, why should a total or near total gastrectomy with esophagojejunostomy correct it using the same jejunal limb? Pellegrini and Ryan[11] have repeated the jejunal manometry studies and disproved this theory.

It serves no useful purpose to label this type of delayed gastric emptying as "Roux-Y syndrome"[12,13] or Albatross syndrome when in fact the delay may be due to some type of obstruction that has not been properly identified. In the final analysis, the delay is not due to a motor disorder of the fundus or the jejunal limb, and in this series the four types of obstruction represent errors in technique, for example, kinked loops, anastomosis too high, incomplete vagotomy, or the gradual development of obstructive pouches.

Currently a total or near total gastrectomy is being recommended for delayed gastric emptying post Roux-en-Y.[13–16,19] Obstruction must play an important role in the delay because in one report 11 of 18 patients with severe vomiting had obstruction at or near the anastomosis due to stomal stenosis or marginal ulcer.[14] In addition, the drawings and radiographs demonstrate overhanging pouches and also an extensive blind pouch. Other reports indicate that most patients have had multiple operative procedures before their total or near total gastrectomy.[15,16] Such patients usually have extensive postoperative adhesions, which are associated with partial obstruction. In a related problem, Cohen and Ottinger[20] described 46 patients with delayed gastric emptying after vagotomy and Billroth II gastrectomy, and 8 of 11 patients reoperated on had obstruction due to kinked loops or adhesions.

In rare instances, total gastrectomy may be the only reasonable surgical procedure, especially in patients who had severely damaged gastric pouches, usually due to multiple previous operations, penetrating wounds, end-stage atrophic gastritis, Zollinger-Ellison syndrome, or impaired blood supply. Conversely, one must consider what is lost in a total gastrectomy, for example, acid, pepsin, intrinsic factor, and the digestive reservoir with the potential for the dumping syndrome and anemias.

Preoperative evaluation must include a detailed history and review of previous operative reports, an UGI series, radionuclide studies for both liquid- and solid-phase gastric emptying, and UGI endoscopy to determine the site and anatomic nature of any obstruction causing functional delay in emptying. Endoscopy also will identify marginal ulcers and bezoars that are usually missed on the other studies. Because motor disorders of the gastric pouch and jejunum have been shown not to be the major problem, one must rule out partial obstruction, which could be corrected by a lesser procedure before resorting to a total gastrectomy.

Conclusion

Delayed gastric emptying after Roux-en-Y procedure may be due to partial obstruction at or near the anastomosis.

The UGI Series and nuclear studies demonstrate the presence and degree of delayed gastric emptying after Roux-en-Y procedure, but not the site and cause of the obstruction.

Upper GI endoscopy defines the site and anatomic nature of the obstruction, the presence of a bezoar or a marginal ulcer, and the options for treatment.

Four types of obstruction other than stomal stenosis have been identified.

In 4 of 42 patients, surgical correction of the obstruction was achieved, and in 6 patients the obstruction was relieved by endoscopic manipulation. Contrary to recent reports, no patient required a total or near-total gastrectomy.

Partial obstruction was the final common denominator in this series for delayed gastric emptying after Roux-en-Y gastrojejunostomy.

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The Utility of Cyclosporine Weaning in Renal Transplantation

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Abrupt conversion of cyclosporine immunosuppression to conventional treatment with azathioprine and prednisone avoids long-term cyclosporine nephrotoxocity, albeit at the cost of a 20% to 40% rejection rate. The authors investigated the benefits and risks of a cyclosporine weaning protocol in 24 cadaveric and 9 live donor kidney recipients treated with a sequential quadruple immunosuppressive protocol. In cadaver kidney recipients, slow tapering of cyclosporine resulted in a 19% ($p < 0.001$) improvement in the glomerular filtration rate, as estimated by the inverse ratio of the plasma creatinine concentration. Cadaver kidney recipients were stratified according to graft function (GFR ratio > 0.76, < 0.76) at the time of cyclosporine discontinuation. In 12 patients with well-functioning grafts, a 24% improvement was observed, whereas in 12 patients with poor graft function, the gain was limited to 13%. Patients with limited graft function tended to have more acute rejection episodes before cyclosporine weaning (0.92 ± 0.64 *versus* 0.42 ± 0.64, not significant). When the 24 cadaver kidney recipients were stratified according to onset of graft function after transplantation (days to plasma creatinine of 250 µmol/L), need for dialysis, panel reactive antibodies (PRA), and duration of cyclosporine treatment, no significant differences in graft function were observed at the onset or end of cyclosporine weaning. Acute graft rejection before cyclosporine weaning was the only variable associated with a significantly lower estimated glomerular filtration rate ratio at the end of cyclosporine treatment (0.83 ± 0.11 *versus* 0.67 ± 0.16, $p < 0.01$). Weaning of cyclosporine was associated with a minimal risk of acute graft rejection. A single patient with stable graft function at the onset of the weaning process experienced an acute but reversible rejection episode 2 months after cyclosporine was discontinued. In summary, gradual weaning of cyclosporine improves graft function, and eliminates the excessive risk of acute graft rejection without the need for additional corticosteroid treatment.

THE UTILITY OF renal transplantation for the treatment of end-stage renal disease has been greatly improved with the introduction of cyclosporine as an alternative immunosuppressive agent. Early and late graft survival rates have improved by about 20%.[1-3] As evidenced by a large body of literature, the toxic effect of the drug on kidney function and kidney morphology is its major drawback, which in the long term may reverse the gains made in the early post-transplant phase.[4,5]

Chronic cyclosporine nephropathy is characterized by a functional component that reverses on discontinuation of the drug and for which changes in renal hemodynamics seem to be responsible.[6] Irreversible morphologic changes occur in renal tubular and vascular structures. Those include isometric tubular vacuolization, presence of megamitochondria, tubular microcalcifications, and most importantly an arteriolopathy that displays similar features as the arteriolar media necrosis occurring in malignant hypertension.[7,8] Tubular atrophy and a patchy fibrosis of the tubulointerstitial space develop as a result of this vascular abnormality.[8]

The clinical management of chronic cyclosporine nephropathy is still disputed. As originally proposed by the Oxford group, a limited use of the drug during the first 3 months after transplantation, and subsequent conversion to conventional immunosuppression with azathioprine and prednisone, significantly improves graft performance while still allowing for a better engraftment rate.[9,10] This approach has been adopted and tested in uncontrolled trials by many other transplant centers.[11-13] Details of the various proposed conversion protocols, however, vary significantly. In some instances, cyclosporine was simply replaced by azathioprine[9,10]; in others, prednisone doses were augmented during the period of conversion,[12,13] and finally, variable overlap periods of cyclosporine and azathioprine treatment were chosen.[11,13]

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The maneuver of abruptly converting immunosuppression from cyclosporine to azathioprine bears the significant risk of triggering acute rejection episodes in 20% to 40% of these patients.[10,11] Our own experience supports the concept that rapid dose reduction or discontinuation of cyclosporine for treatment of suspected cyclosporine nephrotoxicity in many instances is followed by an acute rejection episode. Therefore, we designed a cyclosporine weaning protocol with the aim of slowly reducing and withdrawing the drug, without concomitant changes in prednisone and azathioprine dose. We report here the results of an uncontrolled feasibility study assessing the risks and benefits of cyclosporine weaning observed in 33 patients with stable kidney graft function at the beginning of the tapering process.

Patients and Methods

Patient Population

Between December 1985 and March 1989, a total of 66 patients received kidney transplants at the Royal Victoria Hospital. Fifty-four kidney grafts were from cadaveric donors, and 12 were from living related donors. Three of the sixty-six patients were diabetic. All patients had received at least one leukocyte-poor blood transfusion before transplantation. Thirty-three patients underwent a cyclosporine weaning protocol and were eventually immunosuppressed with azathioprine and prednisone alone (Table 1). The remaining 33 patients were not considered for this protocol because of the following reasons: perioperative death (n = 2), early graft loss (13), documentation before cyclosporine weaning of chronic rejection or recurrent disease by graft biopsy (7), no cyclosporine treatment (4), continued cyclosporine treatment because of third grafts (3); and because of distant domicile from our center (4). Twenty-four and nine recipients of cadaveric and live donor kidneys, respectively, were weaned from cyclosporine as described below.

Immunosuppressive Protocol

A sequential quadruple-agent immunosuppressive regimen was used. Methylprednisolone (500 mg intravenously [I.V.]), and azathioprine (400 mg I.V.) were given perioperatively. A 5- to 7-day course of horse or rabbit anti-lymphocyte globulin was prophylactically administered, starting on the first postoperative day (Lymphoglobulin or Thymoglobulin, one vial per 10 kg body weight; Rhône-Poulenc, Canada). Methylprednisolone was continued at 100 mg/day for 5 days and then tapered such that a maintenance prednisone dose of 20 mg/day was reached at 4 weeks after transplantation. On day 90, the dose was further reduced to 15 mg/day. Azathioprine was continued at a dosage of 125 mg/day. Adjustments were made to maintain the white blood cell count above 4000/mm^3.

TABLE 1. *Demographic Data*

	CAD	LRD
No. of transplants	24	9
M/F	17/7	4/5
Age		
Range	25–57	18–63
Mean	45.5	34.1
First grafts	21	9
Subsequent grafts	3	0
Diabetes mellitus	1	2

CAD, cadaveric donors; LRD, living related donors.

Cyclosporine was withheld until the serum creatinine concentration reached 250 μmol/L. In patients with initial nonfunctioning kidney grafts, anti-lymphocyte globulin was given on alternate days from day 5, until cyclosporine could be started. Cyclosporine was generally initiated at a low dose of approximately 2 mg/kg/day and progressively increased to a maintenance dose of about 5 mg/kg/day. The drug was administered twice daily.

Cyclosporine Weaning Protocol

Weaning of cyclosporine was started 15 days after the prednisone dose was reduced to 15 mg/day, in other words, at day 105 after transplant. The daily cyclosporine dose was reduced by a fixed decrement of 25 mg once every 2 weeks, and completely withdrawn after treatment with 50 mg/day had been tolerated for 2 weeks. The weaning process was of variable length because of the fixed dose reduction.

Assessment of Graft Function

Renal graft function was assessed by plasma creatinine concentrations assuming a stable muscle mass for a given patient during the course. The inverse ratio of the plasma creatinine concentration was used as an estimate of the glomerular filtration rate (eGFR).[14] Estimated GFR ratios greater than 0.76 correspond to plasma creatinine concentrations within the normal range. The ratio of 0.76 was used to stratify patients with "high" and "low" eGFR. The results are reported as mean ± standard deviation. Radionuclide scanning results showed a higher variability and thus were not considered for analysis. Average eGFR ratios and average daily cyclosporine doses were calculated for each elapsed month. In view of a steady weight gain in most patients, it was important to use an estimate of the ideal body weight (IBW), and thus of the lean body mass, which was obtained according to the formula of Broca[15]: IBW in kg = (height in cm − 100).

Acute Rejection

Acute rejection was diagnosed in the presence of clinical signs of decreased urine output, rising plasma creatinine concentration, fever, and new onset hypertension. In four doubtful cases, confirmation by percutaneous biopsy was obtained.

Data Analysis

The time point of cyclosporine discontinuation was arbitrarily designated as day 0. The preceding 6 months and the elapsed time as of March 1, 1990 were included in the analysis. Averaged data are shown as the mean ± standard deviation. Paired t testing was used to compare individual changes with time. Unpaired t tests were applied to compare subgroups of patients, and to test the significance of the correlation between two variables. P values of less than 0.05 were considered statistically significant.

Results

Use of Immunosuppression

For the study group of 24 cadaver kidney recipients, initiation of cyclosporine treatment varied from 2 to 60 days after transplant and was continued for an average of 7.2 ± 3.0 months. Figure 1 displays the progressive decrease in dosage of cyclosporine during the weaning protocol applied during the last 6 months of treatment. As indicated in the Patients and Methods section, cyclosporine doses in milligrams per kilogram per day were calculated on the basis of the estimated ideal body weight. For reasons of comparison, nine recipients of live donor kidneys also were analyzed. In this patient group, the use of cyclosporine treatment was comparable (Fig. 1).

All patients also were treated simultaneously with azathioprine and prednisone starting at the time of transplantation. During months 1 and 2 after transplantation, cadaver kidney recipients received average azathioprine doses of 1.76 ± 0.22 and 1.32 ± 0.49 mg/kg/day, respectively. The mean monthly prednisone dose during the first month after transplant was 33.7 ± 14.1 mg/kg ideal body weight. Live donor kidney recipients tolerated significantly higher doses of azathioprine (1.99 ± 0.25 and 1.62 ± 0.30 mg/kg/day, $t = 2.3945$, $p < 0.05$, unpaired t test) and received significantly less prednisone (26.7 ± 5.5 mg/kg/month, $t = 2.0513$, $p < 0.05$, unpaired t test) early after transplantation.

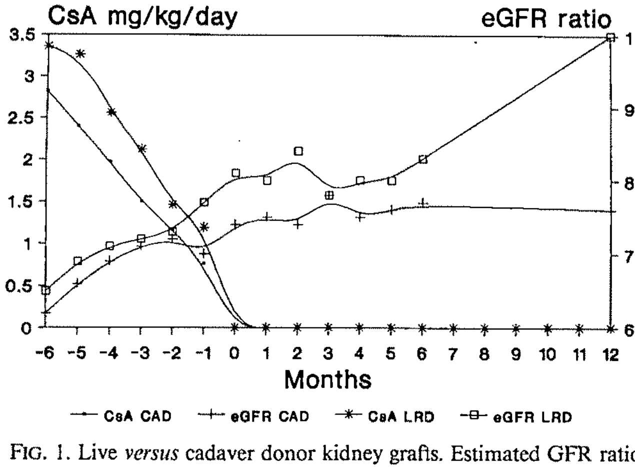

FIG. 1. Live *versus* cadaver donor kidney grafts. Estimated GFR ratios in 24 recipients of cadaver donor kidneys (+) and nine recipients of live donor kidneys (□) in temporal relationship to cyclosporine weaning (CAD/*LRD). Significant improvement of eGFR by 19% ($p < 0.001$) and 25% ($p < 0.002$) during the weaning period (−6 to 0 months), but no significant change of graft function subsequent to cyclosporine withdrawal.

Glomerular Function

Figure 1 demonstrates the progressive improvement in eGFR seen with decreasing daily doses of cyclosporine over a 6-month weaning period. In the 24 recipients of cadaveric kidneys, a 19% improvement (month 6 *versus* 0, $t = 5.7166$, $p < 0.001$, paired t test) in the eGFR was observed with cyclosporine weaning. In comparison, nine recipients of live donor kidneys showed a trend for better graft performance and greater improvement (+25%, month −6 *versus* 0, $t = 3.6952$, $p < 0.002$, paired t test). There was no statistical difference in the mean estimated GFR between cadaver and live donor kidney grafts, however, at any time point before or after cyclosporine discontinuation.

The effect of cyclosporine weaning in patients with high and low eGFR ratios was studied. Patients receiving cadaveric kidneys were stratified according to graft function at the time of complete cyclosporine withdrawal (time point 0). An eGFR ratio of 0.76 corresponds to the upper norm value of the plasma creatinine concentration. Twelve patients each with eGFR ratios of <0.76 and >0.76 composed a "low eGFR" and a "high eGFR" group, respectively. Figure 2 displays the development of graft function in response to cyclosporine weaning in the two groups during a 6-month period. Patients with a low eGFR ratio improved by only 13% (month −6 *versus* 0, $t = 4.4554$, $p < 0.001$, paired t test), and those with a high eGFR by 24% ($t = 4.7029$, $p \ll 0.001$, paired t test). Despite treatment with almost identical doses of cyclosporine per kilogram ideal body weight, the estimated GFR (Fig. 2) was already significantly different at the beginning of the weaning process (high *versus* low eGFR, $t = 2.9379$, $p < 0.01$, unpaired t test). Over a 12-month follow-up period after cyclosporine discontinuation, no further functional improvement of significance was observed in any of the above-mentioned patient groups.

Patients with low eGFR experienced an improvement of graft function until cyclosporine was completely withdrawn. In contrast, the patients with better graft function tolerated an average daily cyclosporine dose of 2.12 ± 0.95 mg/kg ideal body weight without detrimental effect on

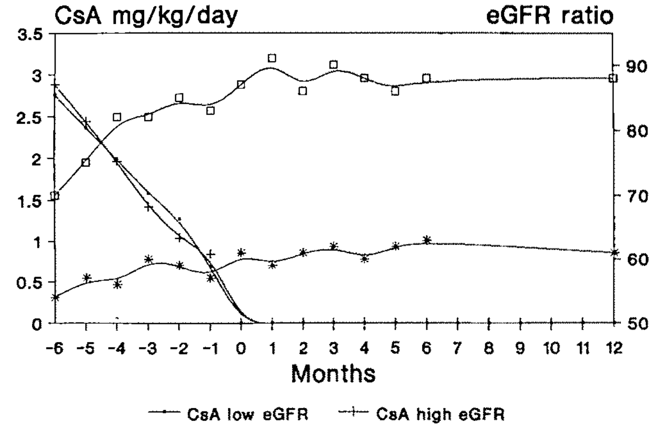

FIG. 2. High and low estimated GFR ratio. Identical weaning of cyclosporine in two groups of 12 cadaver kidney recipients. The two groups are characterized by a high and low estimated GFR ratio at the time of cyclosporine discontinuation. Patients with a high estimated GFR ratio have a significantly better graft function at any time point before and after cyclosporine discontinuation. In patients with a high estimated GFR ratio, the extent of improvement is greater as compared with that of the patients with the poorer graft function (+24% *vs.* +13%).

the estimated GFR (Fig. 2). As summarized in Table 2, patients in the two subgroups received the same immunosuppression during the first month after transplantation and did not differ with respect to other variables.

Long-term Outcome

Six patients with a low estimated GFR, and eight patients with high estimated GFR, were followed after cyclosporine discontinuation for more extended periods of 33.7 ± 5.5 and 34.3 ± 7.0 months, respectively. No significant change in renal function with time was noted in either subgroup of patients (Fig. 3).

TABLE 2. *Other Variables in Patients With Low and High Glomerular Filtration Rates*

	Low n = 12	High n = 20	p
Mean total AZA* (mg/kg/day)	1.72 ± 0.17	1.80 ± 0.26	NS
Mean total PRED* (mg/kg/day)	1.28 ± 0.60	0.96 ± 0.17	NS
Mean ALG doses	4.4 ± 2.5	2.8 ± 2.9	NS
No. of rejections before CsA tapering	0.92 ± 0.64	0.42 ± 0.64	NS
No. of rejections after D/C of CsA	1/12	0/12	
Peak PRA (%)	17.4 ± 22.1	17.5 ± 23.8	NS
Last PRA (%)	10.5 ± 18.8	5.3 ± 9.5	NS
Days to last dialysis	4.7 ± 6.8	2.0 ± 6.1	NS
Patients requiring dialysis	4/12	2/12	NS

* First month.
AZA, azathioprine; PRED, prednisone; ALG, anti-lymphocyte globulin; CsA, cyclosporine; D/C, discontinuation; PRA, panel reactive antibodies.

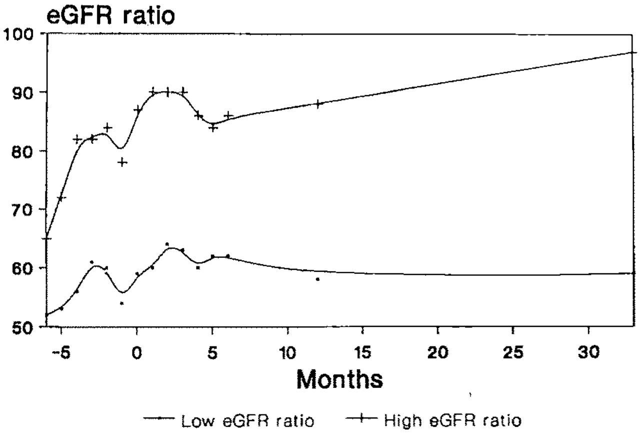

FIG. 3. Long-term follow-up. Extended follow-up of more than 24 months (mean of 34 ± 7 months after cyclosporine discontinuation in 6 and 8 patients with low and high estimated GFR ratio, respectively).

Tubular Function

It was assumed that patients would have a steady monthly intrinsic production of uric acid, and that hyperuricemia would reflect a compromised net tubular excretion in patients with well-functioning grafts. In 24 cadaver kidney recipients, plasma uric acid concentration fell by 11% ($t = 3.5014$, $p < 0.01$) during the period of cyclosporine weaning. When patients were stratified according to their renal function (GFR ratio < 0.76 or >0.76), only those 12 patients with well-functioning grafts experienced a significant reduction in plasma uric acid (−16%, $t = 4.3478$. $p < 0.002$) in response to cyclosporine withdrawal (Fig. 4). In 12 patients with poor graft function, no significant change in plasma uric acid concentration over time was noted. Uric acid concentrations and eGFR ratios, however, were inversely correlated in patients with poorer graft function; no such correlation was noted in patients with well-functioning kidneys (Fig. 5).

Risk Factors

An attempt was made to identify risk factors that might predict either a poor response to cyclosporine weaning or a limited graft function. Hence, recipients of cadaveric grafts were stratified according to variables that are known to influence graft function and outcome. The tempo of onset of graft function after transplantation, in other words, the length of time to reach a plasma creatinine concentration of 250 μmol/L, need for post-transplant dialysis, number of early rejection episodes, presence of PRA at the time of transplantation, and total duration of cyclosporine treatment were included in this analysis. Diabetes mellitus and second grafts were excluded as variables for stratification because of the small number of patients (n < 4).

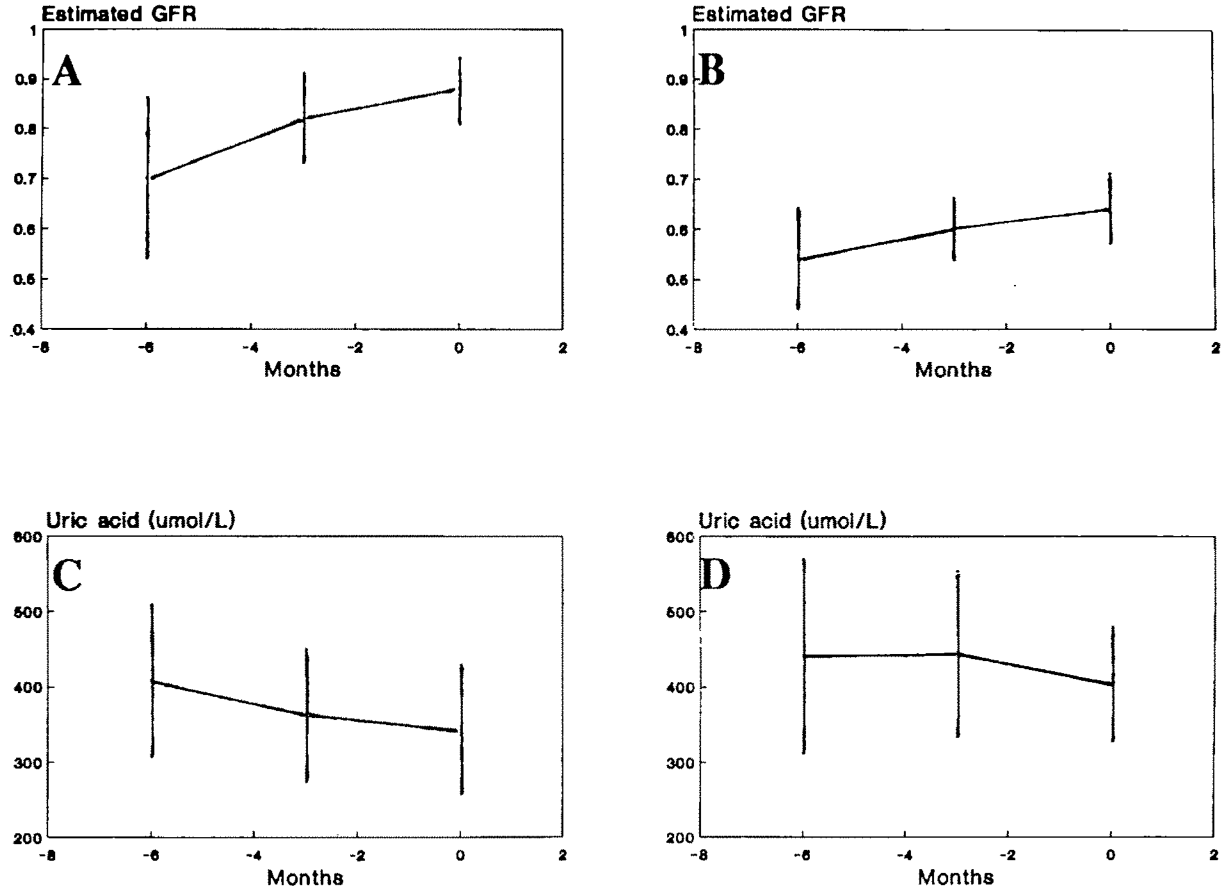

FIG. 4. Changes in plasma uric acid concentration in patients with (A) high and (B) low eGFR ratio. Significant fall in uric acid concentration in patients with (C) high eGFR ($p < 0.01$), but not in patients with (D) low eGFR.

The tempo of onset of graft function had no effect on function during or after cyclosporine therapy. Eleven patients with slow onset of function achieved acceptable graft function in a range from 10 to 59 (24.8 ± 17.6) days, and the remaining 13 patients with a rapid recovery of between 2 and 9 (4.4 ± 2.5) days performed equally well during and after cyclosporine therapy (Fig. 6A). Interestingly, patients with slow recovery of graft function had a significantly higher titer of panel antibodies (15.8 ± 19.4% *versus* 1.2 ± 2.3%, $t = 2.4815$, $p < 0.05$).

Similarly, 18 patients without need for post-transplant dialysis significantly improved eGFR significantly in response to cyclosporine weaning, as did six patients who were dialyzed for an average of 13.3 ± 6.2 days after op-

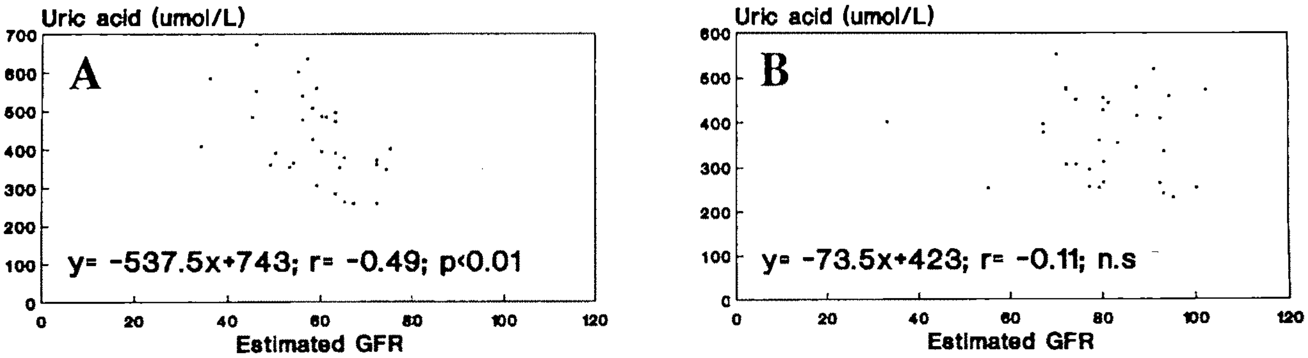

FIG. 5. Correlation of plasma uric acid concentration with eGFR ratio. Correlation of uric acid levels with eGFR ratios is significant in patients with (B) impaired renal function, but not in patients with (A) near-normal graft function.

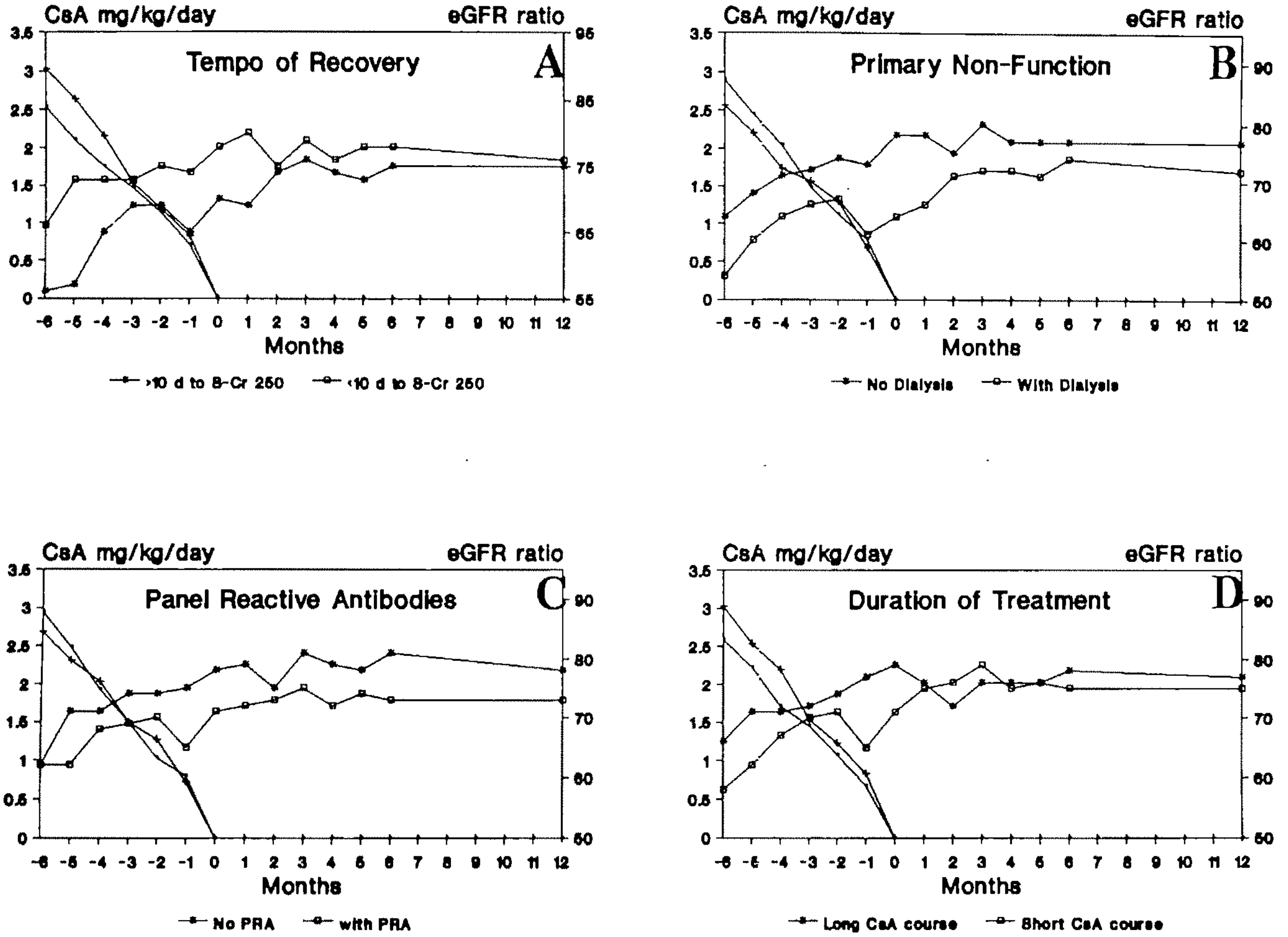

FIG. 6. Weaning of cyclosporine and development of graft function in patients stratified for (A) tempo of onset of graft function (days to plasma creatinine of 250 μmol/L; slow = 10–59 days; rapid = 2–9 days), (B) need for post-transplant dialysis, (C) presence of panel reactive antibodies at the time of transplantation, and (D) duration of cyclosporine treatment. None of these variables affects graft performance.

eration (month −6 *versus* 0, +22%, t = 4.3366, $p < 0.001$, and +19%, t = 7.6500, $p < 0.001$) (Fig. 6B).

The 24 recipients of cadaveric kidney transplants were stratified also according to the presence of PRA at the time of transplantation. Twelve patients with PRA (15.8 ± 18.2%) improved graft function with cyclosporine weaning, similarly to 12 patients without PRA (Fig. 6C). As noted above, however, in patients with a positive PRA titer (2% to 64% panel reactivity at the time of transplantation), onset of graft function was delayed as compared with patients without PRA.

Patients were stratified also according to the duration of cyclosporine treatment. Ten patients received cyclosporine for 10 or more months (10.9 ± 0.9), whereas in the remaining 14 patients the weaning process was terminated within less than 10 months (6.3 ± 2.7, t = 5.9301, $p < 0.001$). Recovery of the eGFR was the same in both groups, indicating that the duration of cyclosporine treatment did not affect the final outcome (Fig. 6D).

The only risk factor predicting poorer graft function was acute graft rejection before cyclosporine weaning (Fig. 7). During cyclosporine treatment, 11 patients never had an early acute rejection episode, and the remaining 13 patients experienced an average of 1.2 ± 0.4 rejections per patient (Table 3). Cyclosporine weaning resulted in a significant improvement of the estimated GFR irrespective of previous rejection episodes (month −6 *versus* 0, +24%, t = 3.3483, $p < 0.01$ and +17%, t = 3.2675, $p < 0.01$, paired t test). The occurrence of acute graft rejection, however, was associated with poorer graft function, both before and after cyclosporine withdrawal. At discontinuation, the mean estimated GFR ratios were 0.83 ± 0.11 and 0.67 ± 0.16, respectively (t = 2.8881, $p < 0.02$). The same significant difference in estimated GFR persisted throughout the first year of follow-up. Patients with acute rejection episodes before cyclosporine weaning were characterized by significantly higher PRA titers and prolonged need for dialysis (Table 3).

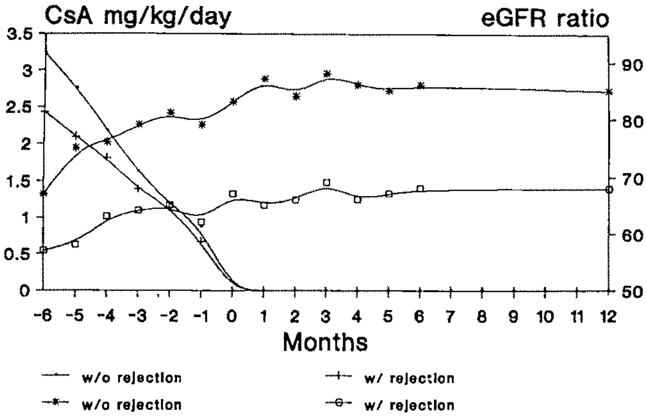

FIG. 7. Effect on renal function of acute rejection episodes before the weaning of cyclosporine in 13 cadaver kidney recipients. At all time points except month −6, the difference of the estimated GFR ratio between patients with and without rejection is statistically significant.

Acute Graft Rejection During and After Cyclosporine Weaning

Among the 33 recipients of cadaveric and live donor kidneys, a single patient experienced an acute but reversible rejection episode 60 days after cyclosporine discontinuation. Cyclosporine was restarted at 3.2 mg/kg per day, a course of increased oral prednisone (total of 1775 mg) was given, and five doses of rabbit anti-lymphocyte globulin administered. The plasma creatinine was 177 μmol/L, before the rejection episode, at the time of cyclosporine discontinuation, and 239 μmol/L 6 months after treatment of this rejection episode.

Discussion

The use of cyclosporine improves the rate of functioning kidney grafts by 15% to 20%.[1-3] Registry data indicate, however, that the loss of kidney grafts during the ensuing years has not been affected by the introduction of the drug.[16] Hence one may hypothesize that cyclosporine has a superior potential to aid engraftment but not to prevent graft loss from chronic rejection, recurrence of the original disease, or late patient death. Limited use of cyclosporine during the first few months after transplantation may reduce its persistent side effects, and also would reduce significantly the costs for immunosuppression.

Previous conversion trials from cyclosporine-based immunosuppression to conventional treatment with azathioprine and prednisone were disappointing because of an unacceptably high rate of acute rejection episodes related to the abrupt cessation of cyclosporine treatment (Table 4). Local experience in a few patients suggested that slow but progressive weaning of cyclosporine was better tolerated and thus might offer an opportunity to achieve a conversion to conventional treatment without excessive risk. Therefore, the feasibility of systematic cyclosporine weaning was studied in 33 kidney recipients who had no signs of chronic rejection or recurrence of the original disease. Four patients with well-functioning grafts were excluded because their distant domicile did not allow a close follow-up. Similarly, three recipients of third grafts were excluded also because the chance for retransplantation appeared slim. The immunosuppressive protocol applied in this study differed in two aspects from commonly used regimens. Firstly, cyclosporine was gradually introduced based on the observation made in heart recipients where this approach successfully prevents cyclosporine-induced acute renal failure. Secondly, cyclosporine was weaned rather than abruptly stopped.

We demonstrate here that slow cyclosporine weaning results in similar functional improvements in cadaveric and live donor grafts (Fig. 1). It was also evident that even minimal cyclosporine doses may impair renal graft function, and that a small but significant improvement can be achieved by discontinuing the drug. Other investigators have reported similar improvements,[11-13] and it appears that a 20% reduction of the eGFR is of functional origin and is not due to a permanent loss of kidney tissue. Stable estimated GFR ratios in 14 patients followed for more than 30 months suggest that cyclosporine weaning may be without detrimental effect on long-term renal function (Fig. 3). Long-term results from conversion trials have not been reported and are therefore not available for comparison.

Two groups of patients could be distinguished with respect to functional improvement. Patients who normalized their estimated GFR ratio (>0.76) with discontinuation of cyclosporine experienced an average improvement of 24%, which was similar to that achieved in live donor kidney recipients. In contrast, patients with a lim-

TABLE 3. *Variables Associated With Acute Graft Rejection*

	Without Rejection n = 11	With Rejection n = 13	p
Rejection episodes*	0	1.2 ± 0.4	
AZA† (mg/kg/day)	1.84 ± 0.23	1.70 ± 0.18	NS
PRED† (mg/kg/day)	1.06 ± 0.56	1.18 ± 0.38	NS
ALG (mean no. doses)	2.8 ± 2.7	4.3 ± 2.7	NS
Peak PRA (%)	7.1 ± 6.7	26.2 ± 27.7	t = 2.4044 p < 0.05
Last PRA (%)	1.6 ± 3.5	13.2 ± 18.7	t = 2.1917 p < 0.05
Days to last dialysis	0.2 ± 0.6	6.0 ± 8.0	t = 2.6053 p < 0.02
Patients requiring dialysis	1/11	5/13	NS

* Before cyclosporine weaning.
† First month.
AZA, azathioprine; PRED, prednisone; ALG, anti-lymphocyte globulin; PRA, panel reactive antibodies.

TABLE 4. *Summary of Major Conversion Trials*

Center	No. of Patients	Time of Conversion (day)	Increase of Steroids	Rejection Rate (%)	Graft Loss (%)	Estimated* GFR Before	Estimated GFR After	Controlled Randomized	Reference
Oxford (trial I)	14	90	No (12) Yes (2)	29	29	NI	NI	Yes	Morris PJ. Transplantation 1983;36:273.[9]
Oxford (trial II)	62	90	No	NI	NI	0.48	0.67	Yes	Chapman JR. Lancet 1985;1:128.[10]
Boston	39	200	No	33	3	0.34	0.47	No	Rocher LL. Transplantation 1984;38:669.[11]
Chicago	27	180	Yes	15	0	0.40	0.47	No	Thistlethwaite JR. Hum Immunol 1985;14:314.[12]
Minneapolis	49	170	No	35	25	0.26	0.48	No	Canafax DM Transplant Proc 1985;17:2677.
Leicester	42	90	No	29	14	0.58	0.83	Yes	Veitch PS. Transplant Proc 1987;19:2017.
Leiden	66	90	Yes	16	6	0.50	0.70	Yes	Kootte AMM. Transplantation 1988;46:677.[13]
Montreal	33	215	No	3	0	0.77	0.90	No	Current study

* Estimated GFR = inverse S-Cr ratio.

GFR, glomerular filtration rate; NI, not indicated.

ited graft function after cyclosporine discontinuation (<0.76) had improved the estimated GFR ratio by a mere 13%. The differential response to cyclosporine weaning raises the question whether all patients or selected subsets thereof should be included in weaning protocols. If functional improvement is the primary reason for cyclosporine withdrawal, only patients with mild impairment of graft function should be subjected to this protocol; if cost considerations are of primary concern, all patients should be included regardless of their initial level of graft function.

We attempted to identify variables that might predict a poor response to cyclosporine weaning. Variables considered for analysis included the duration of cyclosporine treatment, need for post-transplant dialysis, tempo of recovery, presence of PRA (Fig. 6), and donor/recipient matching for human leukocyte antigens (data not shown). The only variable affecting graft function and thus response to cyclosporine weaning was the occurrence of acute graft rejection episodes before cyclosporine weaning. The impact of acute graft rejection on graft performance is quite apparent and more profound than the temporary reduction imposed by cyclosporine treatment (Fig. 7). The occurrence of acute rejection episodes may serve as an indicator to identify the patients who are likely to improve graft function in a significant manner.

Hyperuricemia is encountered significantly more often in patients treated with cyclosporine than in those on azathioprine. Lin et al.[17] recently suggested that retention of uric acid is due to a direct tubulotoxic effect. Weaning of cyclosporine, indeed, was paralleled by a progressive reduction of plasma uric acid concentrations in those patients who normalized their estimated GFR. At the same time there existed, however, no significant correlation between uric acid concentration and eGFR ratio. In contrast, no significant change of uric acid levels were observed in patients with subnormal estimated GFR ratios (Fig. 4). The finding of an inverse correlation of plasma uric acid concentration and eGFR ratio in patients with abnormal graft function at the end of the cyclosporine taper indicates that in a subset of patients, the drug causes hyperuricemia through its limiting effect on glomerular filtration. The lack of such a correlation in patients with mild impairment of renal function, and the progressive reduction of plasma uric acid concentration with cyclosporine tapering support the concept that hyperuricemia results from a tubulotoxic effect on the tubular handling of uric acid excretion. Our data contrast with those reported by Lin et al.[17] in that the tubulotoxic effect could only be discerned in patients with near normal eGFR ratios.

Weaning of cyclosporine in contrast to abrupt conversion bears a minimal risk of triggering acute graft rejection episodes when applied to patients with stable graft function. Our observation of a single acute graft rejection episode among 33 patients contrasts with reports from others[10-12,18,19] who noted the occurrence of such events in 20% to 40% of patients subjected to cyclosporine-azathioprine conversion. More recent evidence indicates that increased corticosteroid doses given during the periconversion period also achieve the goal of minimized risk.[13]

In summary, weaning of cyclosporine is a safe procedure reducing the costs of immunosuppression in all patients, and improving graft performance in a significant manner in those patients who had not undergone a previous acute rejection episode.

Acknowledgments

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Crystalloid is as Effective as Blood in the Resuscitation of Hemorrhagic Shock

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Recently there has been increasing concern over transfusion-related diseases, especially acquired immune deficiency syndrome (AIDS). The authors therefore investigated the efficacy of lactated Ringer's solution (LRS) alone as compared with blood plus LRS resuscitation on body weight change and mortality rate after severe trauma-hemorrhagic shock. Rats, 250 to 310 g (n = 85), had a midline laparotomy performed (*i.e.*, trauma induced), the incision was closed, and a carotid artery, jugular vein, and femoral artery were cannulated. The unrestrained, nonheparinized rats were allowed to recover from anesthesia and were bled within 10 minutes to a mean arterial pressure (MAP) of 40 mmHg. This MAP was maintained by removing more blood until the animal was unable to compensate (maximal bleedout; MB). The MAP was further maintained at 40 mmHg by returning fluid (LRS) until 50% of the MB volume (MBV) was returned. The rats were then resuscitated: group 1 with LRS 4 times the MBV; group 2 with 5 × LRS; group 3 with the shed blood returned + 2 × LRS. There was no difference between the groups in the initial weights, MAP, or hematocrit (Hct), percentage of blood volume removed, time to MB, or time to end of hemorrhage. The final Hct and MAP were higher in group 3 ($p < 10^{-6}$) than in either of the other groups. Body weight gain was greater in group 2 compared with either of the other groups ($p < 0.05$) on day 1 after hemorrhage because of edema, but no differences were seen on subsequent days. There were no differences in the survival of animals in the different groups. These results suggest that there should perhaps be a higher threshold for blood transfusion in the management of severe trauma-hemorrhagic shock than is currently practiced.

TRAUMA CONTINUES TO be a major problem and is the leading cause of death between the ages of 1 and 44 in the United States.[1] One half of deaths occur from exsanguination or central nervous system trauma within 1 hour of injury, and within a further 1 to 2 hours another 30% of deaths occur.[2] These are due to major internal injury.[2] The cornerstone of management of hemorrhagic shock is identification of the source of bleeding and its control, and rapid fluid transfusion to maintain the circulating volume.

Plasma and blood were the replacement fluids of choice until the early 1960s, when the classic work of Shires et al.[3] demonstrated the superiority of a crystalloid solution combined with whole blood over whole blood alone or with the addition of plasma to the shed blood. During the Vietnam war, it was thought that infusions of colloid were necessary to prevent the adult respiratory distress syndrome,[4] but it subsequently has been shown that post-traumatic pulmonary insufficiency is more correlated with sepsis than with the type of fluid used in resuscitation.[5] Current practice in the United States involves transfusing crystalloid in the first instance[1] and using the "transfusion trigger" of a hematocrit (Hct) of 30%[6] to decide when to give blood in addition.

This figure of an Hct of 30% is arbitrary, however, and Hcts as low as 10% to 15% have been well tolerated.[7] Also, there are several problems associated with blood transfusion, including hyperkalemia,[8] acid–base imbalances,[9] etc. The most emotionally charged concern is the transmission of the acquired immune deficiency syndrome (AIDS) virus.[10] In view of this, we investigated the efficacy of crystalloid alone as compared with a combination of whole blood and crystalloid resuscitation on body weight change and death after severe hemorrhagic shock.

Materials and Methods

Hemorrhage Procedure

Male Sprague-Dawley rats (Charles River, Wilmington, MA), 250 to 310 g (n = 85), were fasted overnight but allowed water *ad libitum*. They were lightly anesthetized

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with ether, and the ether cone was removed while a 5-cm midline laparotomy was performed using an electric cautery (*i.e.*, trauma was induced). The organs then were inspected visually to ensure the lack of damage by the cautery. After this, the abdominal incision was closed in layers and a carotid artery (for blood pressure monitoring), jugular vein (for fluid replacement), and femoral artery (for bleeding) were cannulated using PE 50 tubing (Clay Adams, Parsippany, NJ). The portion of the PE tubing inserted into the vessel was narrowed by extrusion to decrease the internal diameter by approximately 50% to prevent clot formation in the tubing. The jugular and carotid catheters were tunneled subcutaneously to the dorsal cervical region. The unrestrained, nonheparinized rats then were allowed to recover from anesthesia, and blood pressure was monitored with a saline manometer through the carotid catheter.

Having recorded the initial mean arterial pressure (MAP) and the Hct, the animals were bled (by withdrawing the blood into a heparinized syringe to prevent clotting) over the course of 10 minutes to an MAP of 40 mmHg. This pressure was maintained by removing more blood in increments of 0.2 mL until the animal was no longer able to maintain its blood pressure (maximal bleedout; MB). The time taken to reach MB was recorded. At this point, the blood pressure was further maintained at 40 mmHg by returning fluid in the form of lactated Ringer's solution (LRS) in 0.2-mL increments until 50% of the shed blood volume was returned in that form (end of hemorrhage; EH). The time taken to EH was recorded.

Resuscitation Procedure

The rats then were divided into one of three groups: group 1 (n = 37) received LRS 3 times the shed blood volume over 45 minutes followed by a further 1× over 60 minutes (total of 4× resuscitation). Group 2 (n = 27) received 3× LRS over 45 minutes followed by a further 2× over 60 minutes (5× resuscitation). Group 3 (n = 21) received the shed blood (kept in the heparinized syringes) back over 45 minutes followed by a further 2× over 60 minutes (blood-back resuscitation).

At the end of resuscitation, the final MAP and Hct were recorded and the animals were lightly anesthetized with ether, decannulated, and the wounds were resutured. They were allowed to recover from the anesthetic and placed in individual cages with free access to food and water.

Parameters Determined

In addition to the parameters mentioned above, the following were noted: The total circulating blood volume (TCBV) was calculated, as previously described by Hauptman et al.,[11] to be 6.12% of the body weight, and the shed blood volume as a percentage of the TCBV was calculated. This was recorded as the percentage total blood volume removed (%TBVR). The animals were weighed daily, and survival was noted each day.

Statistical Analysis

Statistical analyses were performed using one-way analysis of variance (ANOVA), Tukey's, and the chi square test. The percentage data were subjected to arcsine transformation before statistical analysis was performed. Differences were considered significant at $p \leq 0.05$. The results are expressed as mean ± standard error of the mean.

Results

Initial Parameters

There was no statistical difference between the groups in the starting weights (282.8 ± 1.7 g), percentage of blood volume removed (60.9 ± 0.2%), time to maximal bleedout (44.5 ± 0.2 minutes), time to end of hemorrhage (103.7 ± 1.4 minutes), initial hematocrit (41.5 ± 0.3%), or initial MAP (118.9 ± 0.5 mmHg; one-way ANOVA; Table 1). This was true even if the animals were divided into survivor and nonsurvivor subgroups and compared as such within each group or between each group (Tables 2 and 3).

Final Parameters

The final Hct (group 1 = 18.8 ± 0.2%; group 2 = 17.6 ± 0.4%; group 3 = 39.3 ± 0.7%) and the final MAP (group 1 = 88.6 ± 2.1 mmHg; group 2 = 84.1 ± 1.5 mmHg; group 3 = 120.0 ± 2.1 mmHg) were significantly higher in the blood-back group (group 3) than in either of the

TABLE 1. *Comparison of the Parameters Measured in all Animals*

Parameter	Group 1	Group 2	Group 3
Weight (g)	287.8 ± 1.9	275.8 ± 3.5	282.8 ± 2.9
% TBVR	61.1 ± 0.2	60.4 ± 0.3	61.1 ± 0.3
TMB (min)	44.1 ± 0.2	45.1 ± 0.5	44.0 ± 0.4
TEH (min)	107.9 ± 1.4	101.6 ± 3.4	99.1 ± 1.9
IHct (%)	40.4 ± 0.3	43.4 ± 0.5	40.9 ± 0.5
FHct (%)	18.8 ± 0.2	17.6 ± 0.4	39.3 ± 0.7*
IMAP (mmHg)	117.8 ± 0.7	120.7 ± 1.0	118.2 ± 1.0
FMAP (mmHg)	86.6 ± 2.1	84.1 ± 1.5	120.0 ± 2.1*
n	37	27	21

Comparison of initial body weight, percentage of total blood volume removed (% TBVR), time to maximum bleedout (TMB), time to end of hemorrhage (TEH), initial (IHct) and final (FHct) hematocrit, and initial (IMAP) and final (FMAP) mean arterial pressure between group 1 (resuscitation [Rx] with 4 times [×] shed blood volume in the form of lactated Ringer's solution [LRS]), group 2 (Rx with 5× LRS), and group 3 (Rx with blood-back + 2× LRS).

Mean ± SEM.

* = $p < 10^{-6}$ compared with the other two groups, ANOVA, Tukey's test.

TABLE 2. *Comparison of the Parameters Measured in Survivors*

Parameter	Group 1	Group 2	Group 3
Weight (g)	288.9 ± 2.6	275.5 ± 4.2	282.1 ± 4.0
% TBVR	61.0 ± 0.2	60.1 ± 0.4	60.9 ± 0.4
TMB (min)	44.3 ± 0.2	45.2 ± 0.7	44.2 ± 0.5
TEH (min)	109.4 ± 1.5	106.4 ± 4.4	101.2 ± 2.3
IHct (%)	40.4 ± 0.3	43.80 ± 0.8	41.2 ± 0.5
FHct (%)	18.9 ± 0.2	17.6 ± 0.6	39.1 ± 1.0*
IMAP (mmHg)	117.6 ± 0.8	120.1 ± 1.4	116.7 ± 0.9
FMAP (mmHg)	88.9 ± 2.5	83.7 ± 2.3	121.8 ± 2.4*
n	25	14	15

Comparison of initial body weight, percentage of total blood volume removed (% TBVR), time to maximum bleedout (TMB), time to end of hemorrhage (TEH), initial (IHct) and final (FHct) hematocrit, and initial (IMAP) and final (FMAP) mean arterial pressure between group 1 (resuscitation [Rx] with 4 times [X] shed blood volume in the form of lactated Ringer's solution [LRS]), group 2 (Rx with 5X LRS), and group 3 (Rx with blood-back + 2X LRS).

Mean ± SEM.

* = $p < 10^{-6}$ compared with the other two groups, ANOVA, Tukey's test.

crystalloid resuscitation groups (ANOVA, Tukey's test; $p < 10^{-6}$; Table 1). This same trend was seen in the survivor and nonsurvivor subgroups (Tables 2 and 3), but no statistical differences were seen within the groups between survivors and nonsurvivors.

Daily Body Weight and Mortality Rates

On day 1 after hemorrhage, the change in body weight in group 2 (+4.00 ± 1.27%) was significantly higher ($p < 0.05$; arcsine transformation followed by ANOVA; Fig. 1) than in either of the other two groups (group 1 = 1.17 ± 0.72%; Group 3 = −2.42 ± 0.46%). No statistical differences were seen in the percentage weight change each subsequent day after hemorrhage (maximum loss of 7.93 ± 1.32% of the body weight on day 3) between the groups or within the groups between survivors and nonsurvivors.

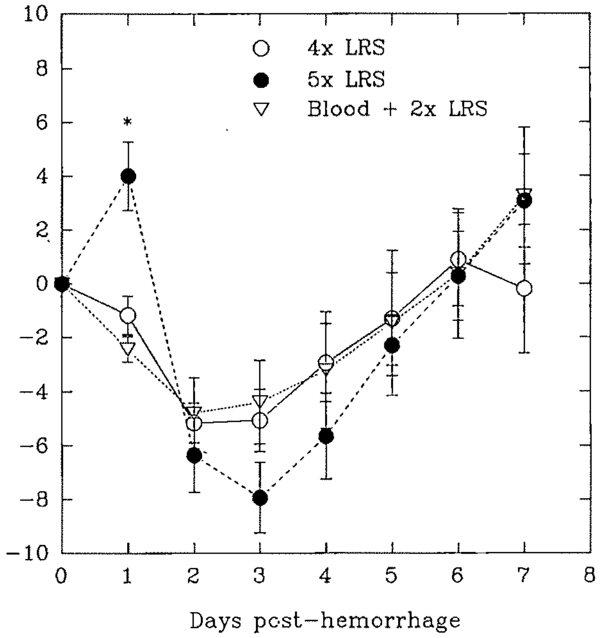

FIG. 1. Daily percentage weight change (mean ± SEM) after hemorrhage and resuscitation (see Materials and Methods for hemorrhage and resuscitation procedure). Group 1 = resuscitation (Rx) with 4 times (X) the shed blood volume with lactated Ringer's solution (LRS), group 2 = Rx with 5X LRS, group 3 = shed blood-back + 2X LRS. The change in weight on day 1 after hemorrhage in group 2 is significantly different (* = $p < 0.05$, arcsine transformation, followed by ANOVA) compared with either of the two other groups. The reason for the initial weight gain in group 2 is the edema due to fluid overload, which is cleared by the second day after hemorrhage. No subsequent statistical differences are seen.

TABLE 3. *A Comparison of the Parameters Measured in Nonsurvivors*

Parameter	Group 1	Group 2	Group 3
Weight (g)	285.7 ± 2.5	276.0 ± 5.6	284.7 ± 2.6
% TBVR	61.3 ± 0.5	60.8 ± 0.5	61.5 ± 0.7
TMB (min)	44.3 ± 0.3	44.9 ± 0.7	43.3 ± 0.8
TEH (min)	104.6 ± 2.7	96.4 ± 4.9	93.7 ± 1.2
IHct (%)	40.4 ± 0.5	49.2 ± 0.7	40.3 ± 1.1
FHct (%)	18.6 ± 0.4	17.7 ± 0.4	39.7 ± 0.8*
IMAP (mmHg)	118.3 ± 1.2	121.4 ± 1.6	122.2 ± 1.7
FMAP (mmHg)	81.7 ± 3.5	84.5 ± 2.0	115.7 ± 3.5
n	12	13	6

Comparison of initial body weight, percentage of total blood volume removed (% TBVR), time to maximum bleedout (TMB), time to end of hemorrhage (TEH), initial (IHct) and final (FHct) hematocrit, and initial (IMAP) and final (FMAP) mean arterial pressure between group 1 (resuscitation [Rx] with 4 times [X] shed blood volume in the form of lactated Ringer's solution [LRS]), group 2 (Rx with 5X LRS), and group 3 (Rx with blood-back + 2X LRS).

Mean ± SEM.

* = $p < 10^{-6}$ compared with the other two groups, ANOVA, Tukey's test.

No statistical differences were seen in the percentage survival of the animals each day after hemorrhage between the groups (group 1 = 67.6%, group 2 = 51.9%, group 3 = 71.4% on day 7 after hemorrhage; arcsine transformation followed by ANOVA, chi square test; Fig. 2).

Discussion

Latta, in 1832,[12] was the first to demonstrate the use of intravenous saline solution to treat hypovolemic shock. In 1899, Crile[13] showed that the maintenance of an adequate circulating volume and central venous pressure with an intravenous infusion of warm saline resulted in reduced mortality rate in experimental hemorrhagic shock. Despite this, the treatment of hypovolemic shock during World War I remained seating the patient upright and bleeding him until he was unconscious because shock was thought to be due to a circulating toxin.[14] In 1930, the demonstration by Blalock[15] that the cause of traumatic shock was hypovolemia, and the experience gained in the management of casualties in World War II, finally dispelled the toxemia theory of shock. Since then there have

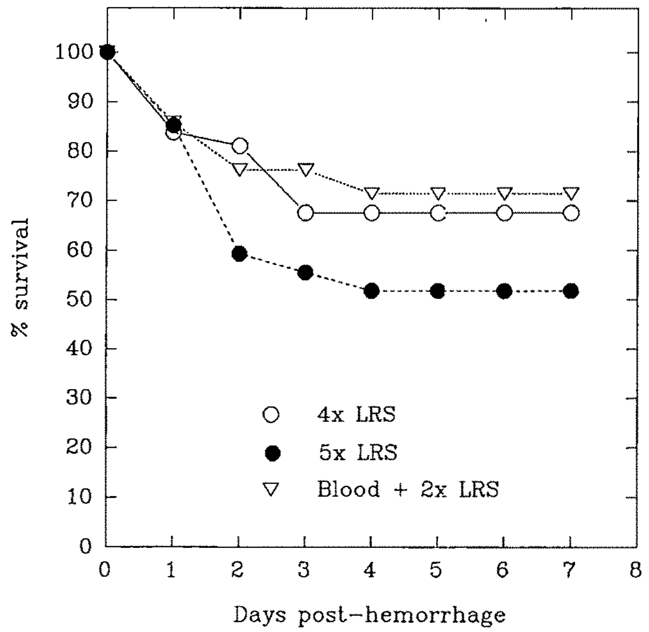

FIG. 2. No differences in the daily percentage of animals still living after hemorrhage and resuscitation were seen between any of the groups (see Materials and Methods for hemorrhage and resuscitation procedure). Group 1 = resuscitation (Rx) with 4 times (X) the shed blood volume with lactated Ringer's solution (LRS), group 2 = Rx with 5X LRS, group 3 = shed blood-back + 2X LRS.

been vogues and controversies as to the type of fluid that should be used for resuscitation.[4,16]

A combination of plasma and blood was the replacement regimen of choice until the early 1960s, when Shires et al.[3] clearly demonstrated the need to replace the extracellular fluid deficit with crystalloid solutions as well as the intravascular fluid losses. Also, Wolfmann et al.[17] showed that survival was markedly improved after hemorrhagic shock if dogs were resuscitated with LRS and donor blood rather than shed blood alone. Jenkins et al.,[18] in 1950, suggested that it was the excessive infusion of salt solutions that was the cause of congestive atelectasis seen frequently after severe hemorrhagic shock. The high incidence of pulmonary insufficiency seen in the severely injured in the Vietnam war led many investigators to believe that infusions of colloid were necessary to prevent the adult respiratory distress syndrome.[19] It subsequently has been shown that post-traumatic pulmonary insufficiency is more correlated with sepsis than with the type of fluid used in resuscitation.[5] Current practice in the United States is to resuscitate with LRS followed by blood as necessary.[1]

There are, however, several problems with the use of blood and blood products, and these are currently cause for concern, especially with the problems associated with transfusion-transmitted AIDS. For this reason, we decided to investigate resuscitation after severe hemorrhagic shock comparing crystalloid alone with a combination of blood and crystalloid.

In this study, we used a model of surgical trauma; in other words, a 5-cm laparotomy incision. This is a significant trauma. Livingston and Malangoni[20] have shown that even a 1-cm skin incision before or after hemorrhage increases infection in the rat. Stephan et al.[21] also have shown that laparotomy alone produces a marked depression in cell-mediated immunity. Studies in our laboratory have demonstrated that whereas the mortality rate was only 10% after hemorrhage and resuscitation in the absence of such trauma, it was 60% if laparotomy was performed before hemorrhage.[22] Thus the model used in this study involved not only hemorrhage, but also significant tissue trauma (5 cm laparotomy), which plays a major role in the outcome of the animals after hemorrhage.

The present study demonstrates that there is no difference in the survival of rats after trauma (laparotomy) and severe hemorrhage when they are resuscitated with LRS alone or with a combination of blood and LRS (Fig. 2). Furthermore, there was no difference in the change in daily body weights at day 1 after hemorrhage (Fig. 1). The reason for the weight gain in group 2 on the first day after hemorrhage was edema due to fluid overload. This was cleared by the second post-hemorrhage day.

The reason for the lack of benefit of blood resuscitation may lie in the viscosity of the circulating blood. Crowell et al.[23] found that increasing the hematocrit above 35% by re-transfusion of blood decreased survival in dogs after hemorrhagic shock, and suggested that the reason for this may be increased blood viscosity. After hemorrhage and resuscitation, we found that there was no significant difference between the final Hcts of the 4× (18.8 ± 0.2%) LRS and 5× (17.6 ± 0.4%) LRS-resuscitated groups, but that of the blood + 2× LRS (39.3 ± 0.7%) resuscitated group was significantly higher ($p < 10^{-6}$). Thus, although there was increased oxygen-carrying capacity in the blood-back group, the benefits appear to have been outweighed by the increase in blood viscosity.

Crowell and Read[24] have demonstrated that there is hypercoagulability after resuscitation of animals with shed blood They suggested that this may be due to release of microthrombi into the circulation. This also may affect the supply of nutrients to the tissues and the removal of the products of metabolism, leading to increased mortality rate in the blood-back group.

We found that the final MAP was significantly higher ($p < 10^{-6}$) in the group of animals resuscitated with blood and LRS (120.0 ± 2.1 mmHg) than in either the 4× (86.6 ± 2.1 mmHg) or the 5× (84.1 ± 1.5 mmHg) LRS-resuscitated groups. This is not surprising because it is known that LRS rapidly enters the extravascular space, and this is one of the reasons Shires et al.[3] recommended its use in the resuscitation of hypovolemic shock. Despite this, however, there was no difference in the survival of the animals in the three groups. Thus, it appears that blood transfusion is not always necessary in the management of hemorrhagic shock, and this is in agreement with the suggestions of other investigators.[6,25]

There has been concern expressed about erythrocyte replacement because transfusion of crystalloids alone will diminish the oxygen-carrying capacity of blood after significant blood loss. Recent studies in this laboratory have indicated that 50% acute hemodilution with LRS in sham-operated animals did not significantly affect cardiac output.[26] Similar observations concerning cardiac output and hemodilution have been reported by others.[27,28] Furthermore, Pelton et al.,[7] in graded hemodilution studies, have shown that Hcts of 10% to 15% in animals subjected to acute hemodilution were well tolerated. Moreover, Mesh and Gewertz,[29] in an intestinal ischemia model, have demonstrated that hemodilution has no adverse effects on oxygen consumption during hypotension and hypoperfusion. Indeed, they suggest that hemodilution may even be beneficial during reperfusion after ischemia.[29]

It should be pointed out that we are not advocating that blood never be used in the resuscitation of hypovolemic shock, but suggesting that the threshold for its use may perhaps be higher than at present. The commonly used "transfusion trigger" Hct of 30%[6] is arbitrary and, as pointed out previously, Hcts as low as 10% to 15% have been well tolerated.[7] This is in agreement with our findings that a hematocrit of 15% to 20% was no more detrimental to the survival of animals subjected to severe trauma-hemorrhagic shock than that of animals with Hcts of 35% to 40%. The results of the study presented here are of significance especially in the present climate of attempting to avoid the transfusion of blood and blood products. There are several potential problems associated with the use of blood and blood products, even if they were not so expensive and in relative short supply.

Platelet and coagulation factor deficiencies are seen in some patients after a massive blood transfusion and may lead to a bleeding diathesis. This is commonly known as "dilutional coagulopathy," but dilution is only a small part of the problem.[30,31] There is an excess of citrate in stored blood to completely bind calcium and prevent clotting and, under normal circumstances, this is rapidly metabolized in the liver. We have recently shown, however, that hepatocellular dysfunction occurs early after hemorrhage and persists despite fluid resuscitation.[32] This may be part of the explanation for the hypocalcemia seen after blood transfusion.[33] The concentration of potassium in the plasma of stored blood increases with time, and hyperkalemia may occur during the rapid phase of transfusion.[8] Banked blood is acidic because of the citrate anticoagulant and becomes more acidic with storage as lactic acid accumulates. This may lead to acid–base imbalances.[9] Storage of blood increases the 2,3-DPG level of erythrocytes and this decreases the affinity of hemoglobin for oxygen, thereby decreasing the delivery of oxygen to tissues.[34] Hypothermia is a complication of the massive transfusion of refrigerated blood, leading to several clinical problems.[35] Stored blood develops particulate debris consisting of microaggregates of platelets, leukocytes, and fibrin, some of which are too small to be removed by standard 170-μm blood infusion filters and may result in pulmonary insufficiency.[36] Antibodies present in the recipient's plasma and directed against foreign transfused red cell antigens can cause serious problems and even death.[37]

Probably the most emotionally charged complication of transfusion of blood and blood products presently is the possibility of transfusion-transmitted diseases. The most serious problem in terms of frequency and complications is non-A, non-B hepatitis. Evidence for the infection can be found in as many as 7% of transfusion recipients within 6 months of the transfusion, and chronic hepatitis develops in as many as 50% of the affected individuals.[38] The most serious problem in terms of public concern is the possible transmission of the AIDS virus.[10] In 1987, 886 cases of transfusion-associated AIDS had been reported,[39] but to put this in perspective, more than 10 million transfusions are given yearly.[6]

In summary, therefore, we compared the weight changes and mortality rates in rats subjected to trauma and severe hemorrhagic shock and resuscitated with either LRS alone or with blood plus LRS. We found that there was no statistical difference in the mortality rate and no differences in weight change at day 2 after hemorrhage between these different resuscitation regimens. These results suggest that the "hematocrit trigger" for transfusion should perhaps be lowered to 20%.

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Treatment of Anal Incontinence by an Implantable Prosthetic Anal Sphincter

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Twelve patients with anal incontinence due to neurologic disease or failure of previous incontinence surgery underwent implantation of an artificial anal sphincter. The system used was a modification of the AMS 800 artificial urinary sphincter. In two patients, infection necessitated removal of the system, and in four patients, eight revisional procedures had to be performed because of mechanical failure. After various modifications of the system, especially reinforcement of the closing mechanism of the cuff, only one case of mechanical failure has occurred. Erosion through the anal canal did not occur. Among 10 patients with the system in function for more than 6 months, the result was considered excellent in 5, with only occasional leakage of flatus, good in 3, who occasionally leaked liquid feces and flatus, and acceptable in 2, in whom the cuff obstructed defecation. It is concluded that implantation of an artificial anal sphincter is a valid alternative to permanant colostomy in patients with anal incontinence due to neurologic disorders and in patients in whom other types of incontinence surgery have failed.

SUCCESSFUL SURGICAL TREATMENT of traumatic anal incontinence has been achieved in approximately 80% of patients by reconstruction of the sphincter and pelvic floor muscles,[1,2] whereas long-term results in patients with idiopathic incontinence have been less satisfactory.[3] In patients with severe destruction of the external anal sphincter or failure of local repair, transposition of skeletal muscle (mainly gracilis or gluteus maximus) has been carried out with acceptable results,[4,5] which have recently been considerably improved by the simultaneous implantation of a neuromuscular stimulator.[6,7]

Anal incontinence due to neuromuscular disorders has not until recently been within the range of surgical or other forms of treatment. We recently reported the first successful implantation of an artificial sphincter for anal incontinence in a patient with a neurologic disease.[8] We report herein the results of the first 12 consecutive implantations.

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Materials and Methods

The artificial sphincter used is a modification of the AMS 800 artificial urinary sphincter (American Medical Systems [AMS], Minneapolis, MN). It consists of three parts (Fig. 1): a cuff placed around the anal canal, a pressure-regulating balloon, and a pump placed in the scrotum or labium majus with which the patient can inflate and deflate the cuff. The cuff is available in lengths of up to 14 cm and with maximum pressure of up to 90 cm H_2O.

Preoperative bowel preparation was performed by whole-gut irrigation, and the operation was performed with the patient in the lithotomy position. Two vertical incisions, each approximately 3 cm long, were made around the anal canal at 3 and 9 o'clock and a tunnel was created around the anal canal by blunt dissection. Pulleys were created posteriorly using the anococcygeal raphe and anteriorly using the raphe of the transversus perinei muscle. This ensured that the cuff would remain in the correct position around the anal canal. The pump was placed in the scrotum or labium majus, and the pressure-regulating balloon extraperitoneally on the left side of the bladder.

Finally, the three components were connected through subcutaneous tunnels with Silastic tubings. Defunctioning enterostomy was not used. Antibiotic prophylaxis with cefuroxime 750 mg, metronidazole 500 mg, and clindamycin 600 mg was instituted on induction of anesthesia and continued with three daily doses for 8 days. During the first 3 to 4 weeks after the operation, the system was left deactivated with the cuff permanently deflated. The patients were kept on a liquid elementary diet for 8 days.

All the patients, in whom the implantation was the only alternative to a permanent colostomy, gave their consent after being informed of the experimental nature of the procedure, including the risk of infection.

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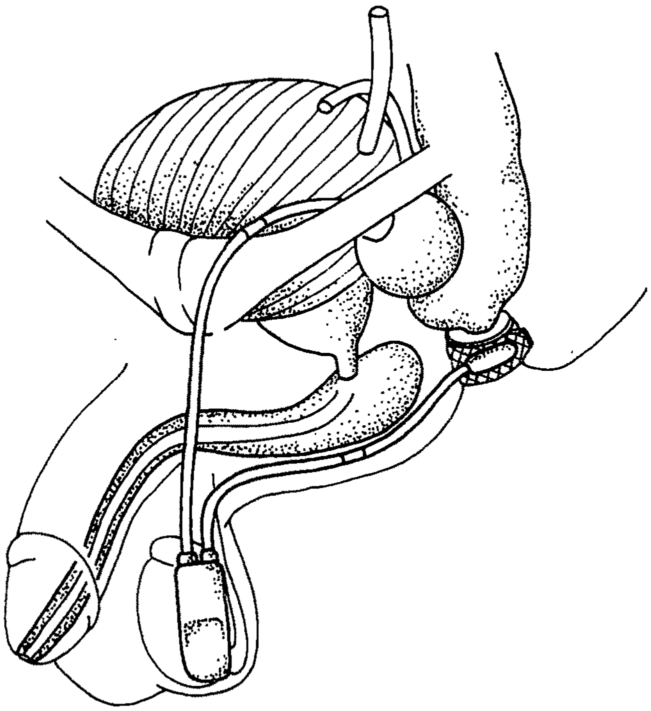

FIG. 1. The artificial anal sphincter in position. The cuff is placed around the anal canal, the pressure-regulating balloon to the left of the bladder, and the pump (control assembly) in the scrotum.

Twelve patients, 9 women and 3 men with ages ranging from 25 to 68 years and suffering from total anal incontinence due mainly to neurologic disorders, had a modified AMS sphincter implanted (Table 1). Nine patients were incontinent because of neurologic disorders. One (with cerebral trauma) had been operated on for anal atresia in childhood with an unsatisfactory result. After cerebral trauma, he had become completely incontinent. One of the three patients with failed previous surgery was still incontinent despite both a previous local sphincter repair and a gracilis transposition.

The median follow-up period was 19 months (range, 6 to 34 months). Preoperative anorectal physiologic parameters are shown in Table 2, together with control values from our laboratory.[9]

Results

The technical results of the implantation are shown in Table 3. Two patients developed infection that necessitated removal of the device 11 and 20 days, respectively, after implantation. One of these patients had the antibiotic prophylaxis discontinued after 3 days because of nausea and vomiting. The other, a young man with chronic nephritis and generalized neuropathy who had refused colostomy, was under immunosuppressive treatment.

TABLE 1. *Underlying Disorders That Cause Anal Incontinence Necessitating Implantation of Artificial Sphincter*

Anal incontinence due to neurologic disorder	9
Prolapsed intervertebral disc	3
Benign spinal tumor	1
Diabetic neuropathy	1
Polyneuropathy	2
Cerebral trauma	1
Myasthenia gravis	1
Failure of previous therapy for anal incontinence	3

TABLE 2. *Preoperative Anorectal Physiologic Parameters*

	Patients	Control value
Anal resting pressure (cm H_2O)	5–20	46–98
Anal squeeze pressure (cm H_2O)	10–48	78–234
Maximum tolerable rectal volume (mL)	100–450	175–450
Pudendal nerve terminal latency (msec)*	2.6–4.8	<2.2

* Examined in only 7 patients with neurologic disease.

TABLE 3. *Technical Result of Implantation of Artificial Sphincter*

Early removal of system	2
Revisional surgery (no. of procedures)	8
Median period with system in function (mo)	19 (6–35)

Revisional surgery for mechanical failure of the system (rupture of the cuff and balloon) had to be performed 8 times in four patients, finally resulting in removal of the device in two. These two patients would have required yet another revision (revision numbers 3 and 4, respectively) due to repeated rupture of the cuff, but at that stage they preferred a permanent colostomy instead. In one patient, infection at the pump site occurred 6 months after implantation. At that time, the patient was receiving prednisone 40 mg daily because of his primary disease (myasthenia gravis). The pump was reimplanted on the opposite side, after which no further infection developed. Erosion of the cuff into the anal canal did not occur in any patient.

The clinical results in the 10 patients in whom the system has been in function for more than 6 months are shown in Table 4. Five patients were completely continent with only occasional leakage of flatus and no obstruction of defecation. Three patients leaked flatus and occasionally liquid feces as well. In two patients with irritable bowel syndrome and frequent periods of constipation, obstruction defecation necessitated frequent use of laxatives and enemas. This was due to the cuff, which in both patients was 10 cm long. One of these patients also leaked fluid feces periodically. Both patients, however, preferred the artificial sphincter to their preoperative condition.

TABLE 4 *Clinical Result of Implantation of Artificial Anal Sphincter in 10 Patients With the System in Function More Than 6 Months*

Excellent	5
Good	3
Acceptable	2
Total	10

Anal canal pressure with the cuff deflated and inflated was 5 to 38 and 40 to 82 cm H_2O, respectively. Defecography with the cuff open and closed was performed in nine patients, demonstrating an anorectal angle of less than 90° with the cuff inflated (Table 5). There was no leakage of the semisolid contrast medium during straining. An example is shown in Figure 2.

Discussion

Implantation of an artificial sphincter for anal incontinence should be considered as an alternative to permanent colostomy. These preliminary results demonstrate that the technique can provide satisfactory function even after long-term follow-up and that the complications most feared, namely infection and erosion, can be controlled. Furthermore, the implantation can be performed without a protective colostomy when adequate bowel cleansing and antibiotic prophylaxis are used.

The high frequency of revisional surgery due to mechanical failures of the system (mainly rupture of the closing tab of the cuff) was limited to the first part of the study, where the unmodified urinary sphincter (AMS 800) was used. After modification of the system for use as an anal sphincter, which included longer and higher cuffs (up to 14 cm in length and 2.5 cm high), higher-pressured balloons (84 to 90 cm H_2O), and stronger closing tabs of the cuff, mechanical failure has only occurred once. Because some diffusion of fluid from the system may take place, another technical advantage has been the construction of a septum pump, which allows refilling of fluid into the system by percutaneous puncture.

Some technical details are important for a satisfactory outcome. It is essential that the cuff is kept in place around the anal canal and does not slide down against the perineal skin, because this will compromise its effect on the anal canal and possibly result in erosion through the skin. This is accomplished by placing the cuff above the anococcygeal raphe posteriorly and above the corresponding raphe anteriorly. If the latter is not present, it may be substituted by the tendinous part of the transversus perinei muscle. In the patient with anal atresia, it was possible to place the cuff above a rudimentary puborectalis muscle.

Erosion of the cuff into the anal canal did not occur in any patient. This is possibly because the cuff was placed around the sphincter muscles, which, in all patients except one, were anatomically intact and thereby constituted a protective layer around the anal canal. In the patient with anal atresia who had no such protective muscles, a layer of fascia from the anterior rectus sheet was encircled around the bowel before placing the cuff. This patient has been followed for 30 months with no sign of erosion. The fact that the anal canal pressure with the cuff inflated was constantly lower than the cuff pressure indicates that the compression force of the cuff is absorbed partially by the muscles and connective tissue around the anal canal.

TABLE 5. *Relationship Between Clinical Results and Anal Canal Pressure and Anorectal Angle With the Cuff Deflated/Inflated*

	Clinical Result		
	Excellent	Good	Acceptable
Anal canal pressure (mmHg)	10–22/62–82	5–38/40–74	8–26/48–68
Anorectal angle (°)	105–120/72–85	100–125/72–85	108–130/80–88

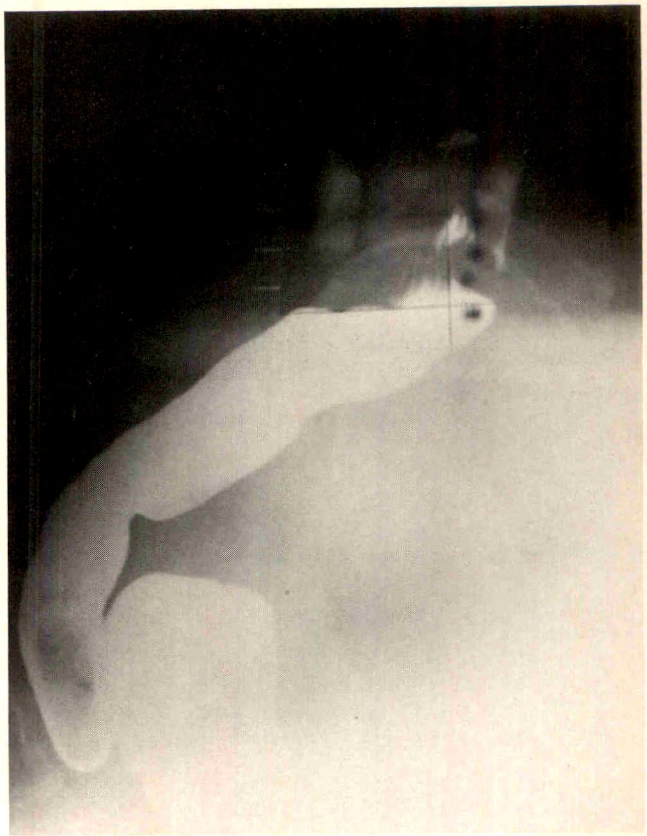

FIG. 2. Defecography during maximum straining with the cuff inflated. The anorectal angle is maintained at approximately 90°.

As in other forms of surgery for anal incontinence, the outcome cannot be correlated convincingly to the anal canal pressure obtained postoperatively with the cuff inflated.[10] Defecography with the cuff deflated and inflated suggests the importance of an obtuse anorectal angle during inflation that act as a flap valve.

The present modification of the artificial sphincter seems to have overcome the initial mechanical problems that necessitated repeated revisional procedures. There should now be no reason to believe that the risk of mechanical failure will be different from that seen with the artificial urologic sphincter, which is at present lower than 5%.[11]

In conclusion, these preliminary results indicate that implantation of an artificial sphincter is a valid alternative to permanent colostomy in patients with anal incontinence due to neuromuscular disease.

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ADVANCES IN SURGICAL TECHNIQUE

Long-limb Gastric Bypass in the Superobese

A Prospective Randomized Study

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This study was designed to determine whether greater diversion of bile and pancreatic secretions away from the functional gastrointestinal tract would produce greater weight loss in superobese patients ($\geq$200 pounds overweight) in comparison with conventional Roux-en-Y gastric bypass (RYGB). During the past 7 years, two modifications of RYGB were prospectively compared in 45 superobese patients: RYGB-1, in which the length of defunctionalized jejunum measured 75 cm, and RYGB-2, in which the defunctionalized jejunum measured 150 cm. Respective mean preoperative weight/body mass indexes were 393 pounds/63.4 for 22 RYGB-1 patients and 404 pounds/61.6 for 23 RYGB-2 patients. Two patients (5%) had nonfatal early complications. There were six late incisional hernias. There were no cases of protein deficiency, hepatic dysfunction, or diarrhea after operation. Mean follow-up was 43 ± 17 months. Postoperative weight loss in pounds and daily calorie intake were compared at 6-month intervals. Weight loss stabilized by 24 months at a mean 50% excess weight lost in RYGB-1 patients and 64% excess weight lost in RYGB-2 patients. Nineteen of 23 RYGB-2 patients achieved at least 50% excess weight lost *versus* 11 of 22 RYGB-1 patients ($p \leq 0.03$). Weight loss was significantly greater at 24 through 36 months in RYGB-2 *versus* RYGB-1 patients ($p < 0.02$). There was no significant difference in either calorie intake or incidence of iron and vitamin B-12 deficiency between the two groups. These data show that gastric restriction and biliopancreatic diversion without intestinal exclusion resulted in significantly greater weight loss than conventional RYGB but did not cause additional metabolic sequelae or diarrhea. This long-limb modification of Roux-en-Y gastric bypass is a safe and effective procedure in patients who are 200 pounds or more overweight.

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THE MINIMUM WEIGHT limit for patients who are considered candidates for surgical treatment of obesity falls in the range of 100 pounds or 100% above so-called ideal weight as defined by standard life insurance tables.[1,2] The concept of "superobesity" has recently evolved to describe a smaller group of patients whose weight far exceeds the minimum weight criteria required for surgical treatment. Successful weight loss in these massive patients has been highly problematic after conventional gastric restrictive operations. This study was performed to determine whether a modification of Roux-en-Y gastric bypass (RYGB) in which bile and pancreatic secretions were diverted more distally in the functional digestive tract would result in greater weight loss in superobese patients than conventional RYGB.

Clinical Material and Methods

During the past 7 years, 45 superobese patients were prospectively randomized to receive one of two modifications of RYGB. Candidates for the study weighed at least 200 pounds more than ideal body weight at the time of their initial preoperative screening examination. All patients were independently evaluated by the surgeon and a clinical nutritionist, (Hallis A. Kenler, Ph.D., R.D.) at each outpatient visit before and after operation. Weight, blood pressure, and pulse rate were recorded at each visit. At the initial screening visit, the medical history was re-

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corded and the clinical protocol was presented to prospective patients by the surgeon. Patients who were interested in participating in the study were given a consent form, which was reviewed again at the time of hospital admission. Patients usually signed the consent form on the evening before operation. Randomization was carried out on the day of operation.

The nutritionist obtained a detailed 1-day recall diet history from each patient at the initial screening visit and at each postoperative visit after the first month. The recall diet analysis included determination of each patient's total daily calorie intake and the relative percentage intake of protein, carbohydrate, and fat. The percentage of daily calories from milk products and sweets was also determined. Sweets intake was further subdivided into solid and liquid categories. Nutritional data were analyzed using the Nutritionist III computer program (N-Squared Computing, Silverton, OR) according to methods described previously.[3]

A chem-21 screen, lipid risk profile, urinalysis, chest x-ray, and electrocardiogram were performed in all patients before operation. A complete blood count; serum levels of vitamin B-12, folate, and iron; and iron-binding capacity were measured before operation and at each postoperative visit beginning at 6 months. Fasting serum glucose and lipid levels were followed at 6-month intervals in patients who had diabetes or hyperlipidemia before operation. Blood samples for measurements of liver function, albumin, and total protein were also obtained at 6, 12, and 18 months after operation. We had hoped to measure 24-hour fecal fat content after operation. However, compliance in obtaining the fecal specimens was so poor that these measurements were dropped from the study protocol.

The operative techniques are shown illustrated in Figure 1. All operations were performed by one surgeon (Robert E. Brolin, M.D.) at Robert Wood Johnson University Hospital. In each case, the volume of the upper gastric pouch was made as small as possible to allow for creation of an 11.4-mm-diameter gastrojejunostomy. Upper pouch volumes were measured in the range of 20 ± 5 mL. The distance between the gastrojejunostomy and jejunojejunostomy was measured on the antimesenteric border with the bowel on a stretch. In RYGB-2, the distance between the jejunojejunostomy and ileocecal junction was determined to be at least as long as the proximal

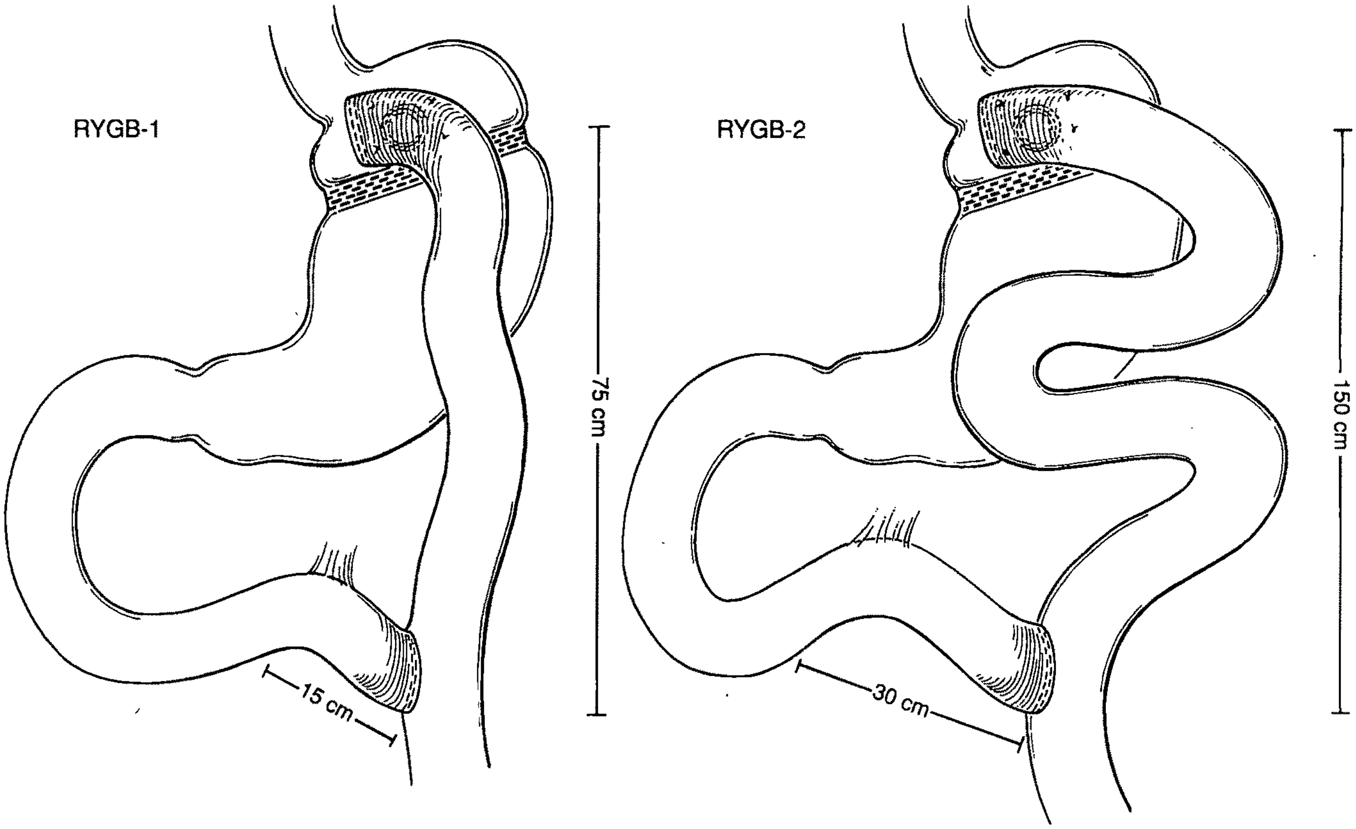

FIG. 1. (Left) In the conventional modification of gastric bypass (RYGB-1), the jejunum was transected 15 cm beyond the ligament of Treitz and the jejunojejunostomy was performed at a measured distance of 75 cm distal to the gastrojejunostomy. (Right) In the experimental group (RYGB-2), the jejunum was transected 30 cm distal to the ligament of Treitz and the jejunojejunostomy was created at a measured distance of 150 cm from the gastrojejunostomy.

measurement between the jejunojejunostomy and the upper gastric pouch. Other details of the operative technique of gastric bypass have been described previously.[4,5]

In the RYGB-1 group, there were 18 women and 4 men, ranging in age from 21 to 60 years, with a mean age of 38.7 years. The mean preoperative weight in RYGB-1 patients was 393 ± 64 pounds, and ranged from 324 to 586 pounds. The mean preoperative body mass index (BMI) was 63.4 ± 10 kg/m^2 and ranged from 48.8 to 94.6 kg/m^2. The mean age of the 8 men and 15 women in the RYGB-2 group was 36.5 years and ranged from 18 to 61 years. In RYGB-2 patients the mean preoperative weight was 404 ± 61 pounds and ranged from 320 to 592 pounds. The mean preoperative BMI was 61.6 ± 9 kg/m^2 and ranged from 51.8 to 89.9 kg/m^2.

After operation, a daily multivitamin supplement containing minerals was recommended for all patients. Patients were instructed to follow a modified liquid diet for the first 4 weeks.[3] At the 4-week visit, patients were given a new diet consisting of a variety of soft solid foods. Subsequent follow-up visits were scheduled at 3-month intervals during the first postoperative year, at 6-month intervals during the second year, and annually thereafter.

Statistical analysis of data was performed using Fisher's exact test, Student's t test and the Wilcoxon rank-sum test for comparisons between the two groups.

Results

Weight Loss and Calorie Intake

Postoperative weight loss in pounds is shown in Figure 2. Weight loss generally stabilized between 12 and 18 months after operation and had stabilized at 24 months after operation in all but one patient. This 33-year-old police officer became an avid weight lifter and occasional jogger after losing more than 150 pounds during the first 18 months after operation. A high level of physical activity probably contributed to his losing 50 more pounds during the third postoperative year. Although mean weight loss in RYGB-2 patients was greater than that in RYGB-1 patients at 6, 12, and 18 months after operation, this difference was not statistically significant. Mean weight loss at 24 and 36 months, however, was significantly greater in RYGB-2 *versus* RYGB-1 patients ($p \leq 0.02$ by unpaired Student's t test). At 24 months, the mean percentage of excess weight lost was 50% in RYGB-1 patients

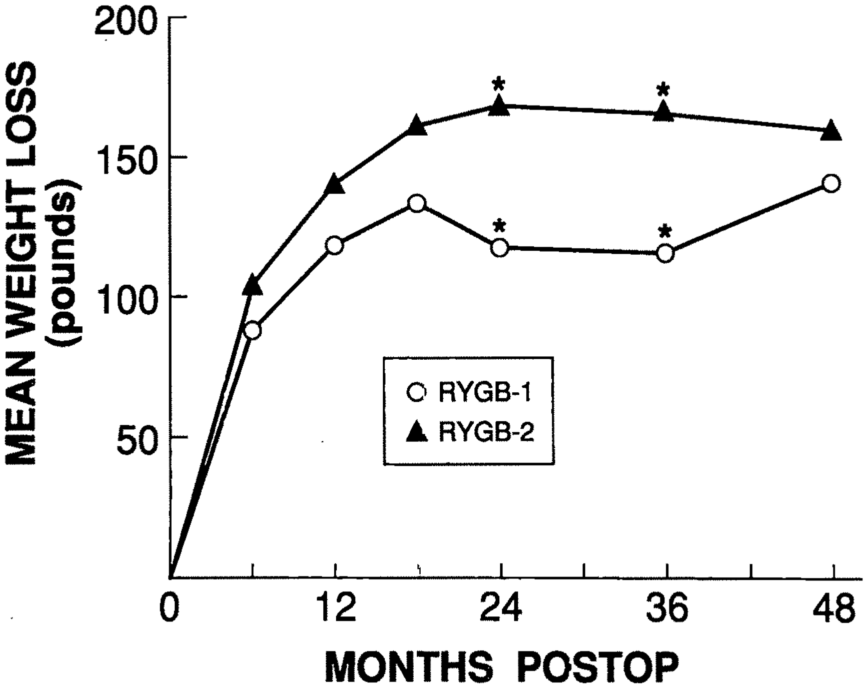

FIG. 2. Postoperative weight loss. The following values correspond with mean ± SD weight loss shown in the graph.

	6 mo	12 mo	18 mo	24 mo	36 mo	48 mo
RYGB-1	88 ± 23	118 ± 35	133 ± 40	117 ± 38*	115 ± 49*	140 ± 63
RYGB-2	104 ± 37	140 ± 41	161 ± 51	168 ± 52*	165 ± 50*	159 ± 70

* Significant difference between groups ($p \leq 0.02$ by unpaired Student's t test).

versus 64% in RYGB-2 patients. Nineteen of the 23 RYGB-2 patients lost at least 50% of their excess weight, whereas only 11 of 22 RYGB-1 patients lost 50% or more of their excess weight ($p \leq 0.03$ by Fisher's exact test).

Postoperative changes in BMI are shown in Figure 3. Body mass index changes in each group closely corresponded with weight loss. Mean BMI in RYGB-2 patients was significantly less than that in RYGB-1 patients at 24 months after operation ($p \leq 0.01$ by unpaired Student's t test). The difference in BMI between the two groups at 36 months approached statistical significance ($p = 0.06$).

Mean daily calorie intake before operation was 3621 ± 1677 calories in RYGB-1 patients *versus* 3828 ± 1120 calories in RYGB-2 patients. Postoperative daily calorie intake is shown in Figure 4. Postoperative calorie intake was significantly decreased *versus* preoperative levels in both groups throughout the duration of the study ($p < 0.001$ by paired Student's t test). Total calorie intake at 6 months after operation was significantly lower in RYGB-1 patients *versus* RYGB-2 patients ($p \leq 0.03$ by Wilcoxon rank-sum test). Daily calorie intake remained somewhat lower in RYGB-1 patients throughout the remainder of the study. The percentage of protein, carbohydrate, and fat in the diet was similar in RYGB-1 *versus* RYGB-2 patients after operation. There was also no significant difference in consumption of sweets or milk products between the two groups.

Improvement of Medical Problems and Lifestyle

There were 101 medical problems identified before operation in the two groups, as shown in Table 1. Only 3 of the 45 patients (6.6%) did not have obesity-related medical illnesses before operation. Hypertension, defined as a resting diastolic blood pressure of 90 mmHg or greater, was the most common problem and was recognized in 73% of these patients. Venous stasis was characterized by skin discoloration and brawny edema in the lower legs. Arthritis invariably involved weight-bearing joints. Congestive heart failure was typically associated

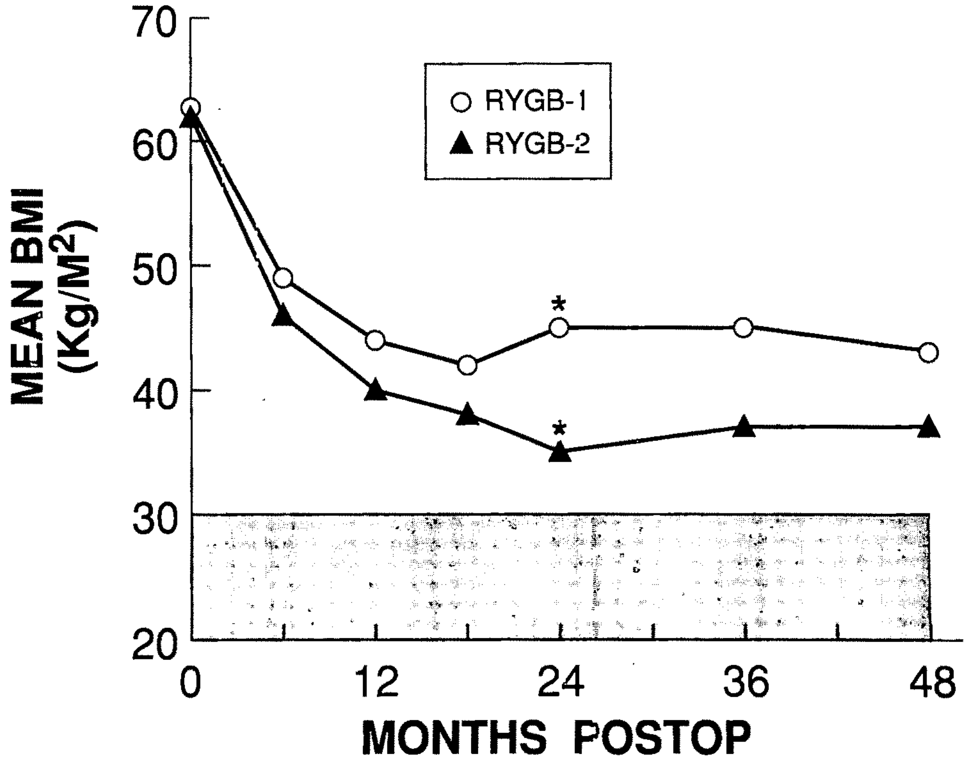

FIG. 3. Postoperative changes in BMI. The shaded area corresponds with the BMI range below Bray's minimum definition of obesity (BMI ≥ 30). The following values correspond with mean ± SD BMI shown in the graph.

	6 mo	12 mo	18 mo	24 mo	36 mo	48 mo
RYGB-1	49 ± 9	44 ± 8	42 ± 11	45 ± 13*	45 ± 14	43 ± 10
RYGB-2	46 ± 8	40 ± 9	38 ± 7	35 ± 5*	37 ± 6	37 ± 11

* Significant difference between groups ($p \leq 0.01$ by unpaired Student's t test).

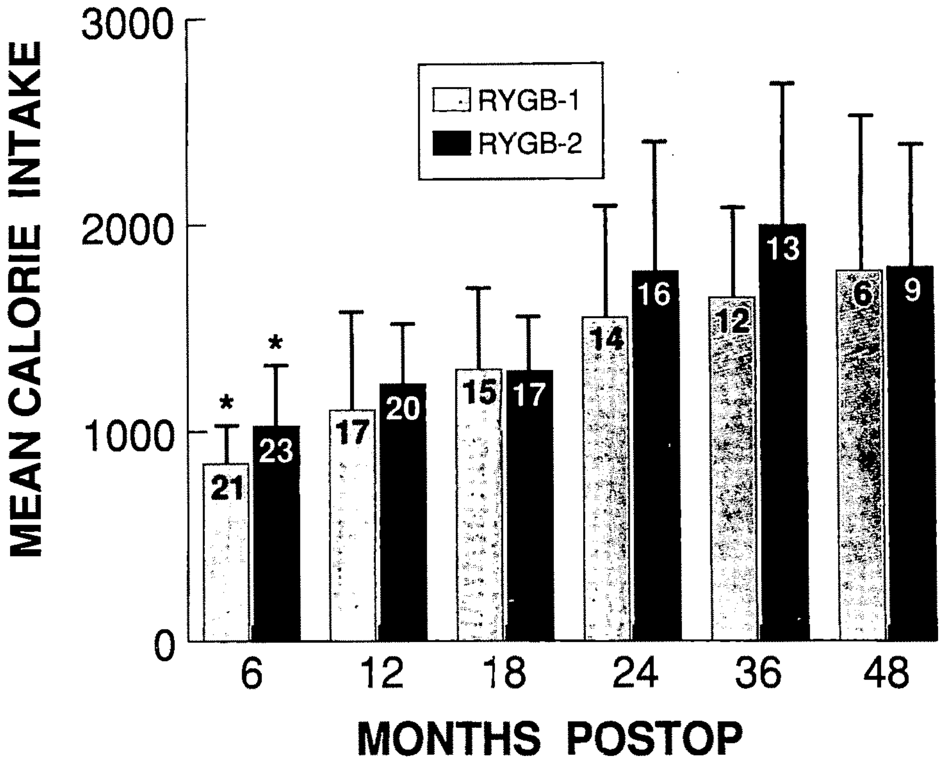

FIG. 4. Postoperative calorie intake. The numbers within bars represent the number of patients followed at each interval. The following values correspond with mean ± SD calorie intake in graph.

	6 mo	12 mo	18 mo	24 mo	36 mo	48 mo
RYGB-1	848 ± 181*	1102 ± 482	1296 ± 392	1549 ± 528	1643 ± 434	1722 ± 742
RYGB-2	1026 ± 290*	1225 ± 298	1285 ± 271	1770 ± 618	1990 ± 679	1789 ± 585

* Significant difference between groups ($p \leq 0.03$ by Wilcoxon rank-sum test).

with cardiomegaly, edema of the lower extremities, and elevated pulmonary artery wedge pressure measurements. All of the six diabetic patients were resistant to large doses of insulin. The five patients with asthmatic bronchitis were taking bronchodilators and had exertional dyspnea. Cardiac arrhythmias included multifocal premature ventricular contractions in three patients and atrial fibrillation in two patients. Patients with sleep apnea syndrome had elevated resting arterial carbon dioxide partial pressure levels and multiple apneic spells identified during polysomnographic studies.

Table 1 also shows the response of the 101 medical problems to weight loss at 24 months after operation. Improvement in congestive heart failure, arthritis, and asthmatic bronchitis included reductions in both symptoms and medications. Medical illnesses were either resolved or improved in all but four patients (9%). Each of these patients had unsatisfactory weight loss, with excess weight loss ranging from 33% to 47% at 24 months after operation.

Weight loss also had a positive socioeconomic effect on many of these patients. Seven of 11 patients (64%) who were receiving welfare or medical disability before operation subsequently became gainfully employed. Although most patients claimed greater satisfaction in their sex and social lives after operation, divorces among women outnumbered marriages by three to two. There was one divorce among the nine men who were married before operation. One man was married 18 months after RYGB-2. Two other men who were unmarried before operation remain single.

Postoperative Complications

There were three early postoperative complications in two patients. One patient had a major skin wound dehiscence that required operative closure. The other patient had a pulmonary embolus 10 days after a major wound infection developed. There were no perioperative deaths.

Late complications included six incisional hernias that

TABLE 1. *Incidence of Obesity-related Medical Problems and Response to Weight Loss at 24 Months*

Problem	No.	(%) of Total Patients	Resolved	Improved	Unchanged
Hypertension	33	73	22	8	3
Venous stasis	20	44	5	12	3
Congestive heart failure	10	27	2	8	2
Arthritis	11	24	3	8	0
Hyperlipidemia	6	13	1	4	1
Diabetes	6	13	3	3	0
Asthmatic bronchitis	5	11	4	1	0
Cardiac arrhythmia	5	11	0	4	1
Sleep apnea	3	7	3	0	0
Total no. (%)	101 (100)		43 (43)	48 (47)	10 (10)

Numbers in the third column are percentages of each problem in the entire series of 45 patients. Medical problems were considered resolved when they were controlled without medication and improved when they were controlled with reduced doses of medication.

were recognized between 6 and 24 months after operation, and one marginal ulcer. Postoperative vitamin and mineral deficiencies were noted in 16 patients who had RYGB-1 and in 17 patients who had RYGB-2. Three patients in each group had folate deficiency that was easily corrected by addition of a daily multivitamin supplement. Five patients in each group had vitamin B-12 deficiency. Nine of the ten vitamin B-12 deficiencies responded to additional oral B-12 supplements of 500 μg daily. Iron deficiency was noted in 11 RYGB-1 patients and in 13 RYGB-2 patients. All but 1 of these 24 patients were women. Nine of the 11 women with iron deficiency in the RYGB-1 group had a microcytic anemia. In the RYGB-2 group, iron-deficiency anemia was recognized in 6 of the 12 women with iron deficiency. Twelve of the 24 patients with iron deficiency responded to oral iron supplements of 600 or 900 mg daily. Two of the 12 patients who did not respond to oral iron administration were given intramuscular injections of Imferon (Fisons, Bedford, MA). Both of these women had moderately severe iron-deficiency anemia (hemoglobin $\leq$ 10 g/dL) and are still receiving Imferon injections. The remaining 10 patients with uncorrected iron deficiency are currently taking oral supplements.

There were no cases of postoperative protein deficiency or hepatic dysfunction. One RYGB-2 patient who was taking furosemide 80 mg daily for hypertension and congestive heart failure had transient hypokalemia that was corrected by increasing her oral potassium supplement. No patient had diarrhea after operation. Most patients reported having one small formed stool per day. Several patients in the RYGB-2 group reported having two or three semisolid stools during the first several months after operation. By 1 year, however, the consistency of stools in these patients gradually increased, and the frequency decreased to normal levels.

The only late death occurred at age 53 in a RYGB-1 patient who died of congestive heart failure 6 years after operation. This man was reported to be a reformed alcoholic who weighed 449 pounds and had diabetes, hypertension, and biventricular heart failure at the time of operation. During the first postoperative year, he required a femoral popliteal bypass and subsequent amputation of his right foot for progressive diabetic atherosclerotic disease despite losing more than 150 pounds. His symptoms of congestive heart failure were notably improved during the first 18 months after operation, until he resumed drinking. After resumption of alcohol intake, he gained weight rapidly and had fulminant anasarca at the time of his death.

Follow-up

Postoperative follow-up in these patients was difficult. Mean follow-up was 43 ± 17 months and ranged from a minimum of 12 months to a maximum of 86 months. All patients were followed in the outpatient clinic at Robert Wood Johnson University Hospital through their 6-month visit. The number of patients followed at each interval through 48 months is shown in Figure 4. Several patients missed interval visits but were not lost to follow-up. Three RYGB-1 patients did not return for follow-up at our medical center after the first postoperative year. One of these patients was subsequently followed through a medical clinic in Elizabeth, New Jersey, for 36 months. Another patient refused to keep numerous follow-up appointments after 6 months. Her weight after 18 months was provided by her gynecologist, and was recorded as 351 pounds because it exceeded the 350-pound limit of his office scale by an unknown amount. The remaining patient moved to Texas after 12 months and was followed locally by a physician who provided follow-up data for another 12 months. Another patient in the RYGB-1 group was withdrawn from the study after 24 months, when she was converted to a distal gastric bypass because of unsatisfactory weight loss. Two other patients (one in each group) were lost after moving out of state during the fourth postoperative year. One patient in the RYGB-2 group was excluded from the study after full-blown acquired immune deficiency syndrome developed 16 months after operation.

Three women became pregnant during follow-up, including a 35-year-old woman in the RYGB-1 group who became pregnant 6 months after operation, and two women in the RYGB-2 group, ages 19 and 29, who became pregnant during the latter part of the second postoperative year. During pregnancy, the weight of these three women was not entered in the study. Their weights were again recorded 3 months after delivery. The postpartum weight of each patient was less than the preconception weight. All three pregnancies were uncomplicated and ended with normal labor and delivery of four healthy infants (One woman had twins.).

Discussion

Defining Superobesity

Our arbitrary definition of superobesity at 200 pounds or more greater than ideal weight was chosen to reflect a minimum weight limit that corresponded to twice the minimum weight criterion (≥100 pounds overweight) that is used to define morbid obesity. In 1987, Mason et al.[6] classified patients who weighed 225% or more above ideal weight as "superobese," and suggested that these patients required a separate outcome analysis from their lighter morbidly obese patients, who weighed between 160% and 225% of ideal weight before vertical banded gastroplasty.[6] The basis of their recommendation was their finding that the heaviest patients lost a significantly lower percentage of their excess weight despite losing a significantly greater quantity of weight in comparison with the lighter patients. Benotti et al.,[7] Sugerman et al.,[8] Yale,[9] and MacLean, Rhode, and Forse[10] have subsequently used the Mason group's definition of superobesity (≥225% of ideal weight) in their reports of gastric restrictive operations. Each investigator likewise noted a lower percentage of excess weight loss in the superobese despite greater weight loss in pounds *versus* the lighter patients.[7-10]

The distinction between morbid obesity and superobesity can be justified on several grounds. First, the incidence of coexisting medical problems and overall health risk is substantially greater in the superobese.[2,5] Second, the likelihood of successful weight loss in the superobese is significantly lower than in the lighter patients after conventional gastric restrictive operations.[6,8] Hence, the distinction between morbid obesity and superobesity could be used to justify controlled prospective trials of operations that combine gastric restriction with malabsorption with the goal of improving weight loss without increasing the postoperative complication rate. It seems clear that the heaviest patients must lose more weight to achieve a level that would represent a valid reduction in their actuarial mortality risk.

The apparent paradox between differences in absolute quantity of weight loss and percentage of excess weight loss in superobese patients is readily explained by the criteria used to define successful weight loss after obesity operations. We have previously shown that the incidence of successful weight loss can be determined by both the patients' preoperative weight and the criteria used to define "success."[5,11] Our analysis affirmed that superobese patients lose more pounds but stabilize at a significantly greater percentage over ideal body weight than do the lighter morbidly obese patients. Moreover, there were statistically significant differences in the incidence of successful weight loss within the same group of patients that were solely determined by the criteria used to define "success." Loss of 50% of the excess weight has been used as a criterion to define "success" in several previous reports of bariatric operations.[5,7,12] Because the excess weight is the calculated difference between the ideal and preoperative weight, in the heaviest patients, excess weight loss is an intermediate outcome measure between weight loss calculated as a percentage of the preoperative weight *versus* a percentage above ideal weight.

The National Institutes of Health (NIH) Consensus Development Panel on obesity surgery recently recommended use of the BMI rather than a quantity or percentage of overweight in both preoperative patient selection and in reporting postoperative results.[13] The NIH panel established the minimum weight limit of "morbid" obesity at a BMI of 40 kg/m^2. Bray[14] has defined "obesity" at a BMI of at least 30 kg/m^2, which closely corresponds to 20% above the median of the recommended midpoint weight range for height according to the 1983 Metropolitan Life Insurance tables. Normal BMI has been calculated in the range of 21.6 to 24.4 kg/m^2, depending on frame size.[15] Because BMI expresses the magnitude of overweight for height as a single number, the variability inherent in expressing weight loss in terms of percentage of the preoperative weight or excess weight is avoided.

MacLean, Rhode, and Forse[10] and Benotti et al.[7] recently established a minimum BMI definition of superobesity at 50 kg/m^2.[7,10] The mean BMI at the point of maximum weight loss among superobese patients in the current study was 42 ± 11 in RYGB-1 patients and 35 ± 5 in RYGB-2 patients. Calculated BMI for patients who are approximately 50% overweight falls in the range of 34 to 36.5 kg/m^2. The BMI of 42 kg/m^2 recorded in RYGB-1 patients at 18 months after operation corresponds to approximately 85% overweight and exceeds the BMI limit of 40 kg/m^2 that was recently established by the NIH Consensus Development Panel as the minimum definition of morbid obesity. Only 7 (16%) of the 45 patients in the current series stabilized at a BMI less than or equal to 30 kg/m^2 (approximately 20% overweight), and only one reached a BMI of 25 kg/m^2 or less (normal weight) at the nadir of weight loss. These BMI data provoke the question of what are realistic and worthwhile weight loss goals for superobese patients after gastric restrictive procedures. It is probably unrealistic to expect that patients with a preoperative BMI of 50 kg/m^2 or greater should reach a BMI of less than 30 kg/m^2 after weight stabilization.

Combining Gastric Restriction With Malabsorption

In 1976, Scopinaro et al.[16] introduced biliopancreatic bypass (BPB), which combines a modest amount of gastric restriction with intestinal malabsorption. This group's early technique included transection of the small bowel at its midpoint and anastomosis of the proximal ileum to a 400-mL capacity gastric remnant after the distal stomach was removed. The jejunum is totally excluded from digestive continuity with the distal end anastomosed end-to-side to a "common channel" of ileum at a point 50 cm proximal to the ileocecal junction. The goal of biliopancreatic bypass was to provide temporary limitation of food intake caused by rapid emptying of the gastric remnant in conjunction with persistent malabsorption selective for fat and starch due to diversion of biliary and pancreatic secretions into the distal ileum.[16,17] Scopinaro et al. initially tested BPB in dogs and found that a 20-cm–long common tract consistently produced diarrhea, hypoproteinemia, and electrolyte imbalance, whereas a 35- to 40-cm–long common tract did not produce these sequelae.[17] Dogs with a 40-cm–long common channel, however, had a 35% weight loss and a 40% or greater increase in fat excretion *versus* control animals. Scopinaro and colleagues have subsequently modified their original operation by further reducing gastric capacity to approximately 200 mL in superobese patients (the so-called very little stomach modification) and have lengthened the common channel in less obese patients to decrease the incidence of malabsorption-related sequelae.[18]

Although weight loss with the Scopinaro group's BPB bypass has been excellent, it occurs at the expense of a variety of serious postoperative complications. Major perioperative complications have been reported in 8% to 10% of patients after BPB, including a mortality rate of between 1% and 2%.[16,18] The incidence of major metabolic complications during the first postoperative year has been alarmingly high, and includes a 30% incidence of anemia, a variety of vitamin and mineral deficiencies, and a 20% incidence of hospitalization for treatment of protein-calorie malnutrition.[16] Sugerman et al.[19] recently reported preliminary results of a prospective comparison of BPB with conventional RYGB in superobese patients.[19] Their 25 BPB patients had a 50% incidence of serious postoperative complications and metabolic sequelae, including two deaths. One of these deaths resulted from hepatic failure. Although weight loss at 1 year was significantly greater after BPB in comparison with conventional RYGB, Sugerman et al. concluded that the incidence and severity of complications after BPB was too great to justify its use as a primary operation for treatment of patients with superobesity.

The RYGB-2 modification of gastric bypass used in the current study differs substantially from the Scopinaro et al. BPB in that only 30 cm of small bowel is totally excluded from digestive continuity. This technique was designed to induce greater malabsorption of dietary fat without producing the protein malabsorption or clinically overt malnutrition that have been associated with the Scopinaro group's operation. Because mean calorie intake was consistently greater in RYGB-2 *versus* RYGB-1 patients, the superior weight loss in the RYGB-2 group may be attributed to greater fat malabsorption resulting from more distal diversion of bile and pancreatic secretions in the functional digestive tract. Unfortunately, our inability to measure fecal fat after operation coupled with the absence of an on-site clinical research center precluded verification of the fat malabsorption hypothesis. As an afterthought, we measured serum carotene levels in many of these patients. Although serum carotene levels in both groups were in the low normal to subnormal range, lack of parallel collection of samples throughout the entire study did not permit valid comparison of these data.

Risk–Benefit Analysis

A valid analysis of any obesity operation probably requires postoperative follow-up of at least 5 years. The pitfalls of assessing the effectiveness of operations with only 2 or 3 years' follow-up were clearly demonstrated by both jejunoileal bypass and horizontal gastroplasty in the early era of bariatric surgery. Hence, the results of this prospective series could be considered somewhat preliminary. Although the mean 43-month follow-up period is probably sufficient to validate the difference in weight loss between these two modifications of RYGB, there was a similar pattern of recidivism in RYGB-1 and RYGB-2 patients after weight stabilization. The loss of statistical significance in weight loss between the two groups at 48 months after operation was due to both the smaller number of patients followed at this interval and the fact that two of the most successful RYGB-1 patients were among the six patients in that group who were evaluated at 48 months. Weight loss maintenance in both groups was related to postoperative calorie intake in that recidivism generally occurred when calorie intake exceeded 1500 calories per day in women and 1800 calories per day in men. The lack of statistically significant differences in calorie intake between the two groups after 6 months following operation is primarily due to the large variation in daily calorie intake recorded among individual patients in both groups with longer postoperative follow-up (Fig. 4). Most of these added calories were in the form of either high-calorie liquids, soft junk food, or both, rather than as larger portions of mealtime foods. Patients who consciously restricted their intake of high-calorie liquids and soft junk food invariably maintained their weight loss.

Improvement of both coexisting medical problems and general lifestyle were dramatic among patients who lost substantial amounts of weight. The 90% incidence of improvement or resolution of medical problems in these patients was substantially greater than the incidence of successful weight loss, per se, in that 15 patients (33%) did not lose at least 50% of their excess weight. Moreover, there was virtually no regression of improved or resolved medical problems in patients who maintained satisfactory weight loss for the duration of the study. Conversely, improvement of medical problems was limited or transient in several patients who did not lose 50% of their excess weight. These results suggest that 50% excess weight loss is a useful measure of success in superobese patients, despite the fact that many of these patients remain 50% overweight after stabilization.

The 4.4% early complication rate in the current study compares favorably with the incidence of early postoperative complications reported by other surgeons in unselected series of gastric bypass patients.[7,9,20] This complication rate is also similar to the early morbidity rate previously reported in our lighter bariatric surgical patients.[5] Conversely, the 13% incidence of late incisional hernias in the current series is nearly twice as high as the incidence of postoperative hernias in our lighter bariatric patients. The 73% incidence of postoperative vitamin and mineral deficiencies in this study is somewhat higher than the overall incidence of these deficiencies previously reported in patients after conventional RYGB.[21,22] There is evidence, however, suggesting that the incidence of these metabolic deficiencies increases with longer follow-up after conventional RYGB.[23] There was no difference in the incidence of postoperative metabolic deficiencies between RYGB-1 and RYGB-2 patients. All of the postoperative vitamin and mineral deficiencies in this series were managed on an outpatient basis. Only two patients required injections rather than oral supplements. Patient noncompliance in regularly taking multivitamin supplements and in returning for scheduled follow-up visits contributed to the development and progression of many of these deficiencies.

In summary, this prospective study shows that gastric restriction combined with a modest degree of biliopancreatic diversion resulted in significantly greater postoperative weight loss in superobese patients than did conventional RYGB. Because only 30 cm of jejunum is excluded from the functional digestive tract, protein-calorie malnutrition and persistent diarrhea were not observed after the long-limb modification of RYGB. It appears that this long-limb modification of RYGB poses no greater risk of complications than the conventional technique.

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The Genuine Southern Surgeon

JOHN OCHSNER, M.D.

From the Department of Surgery, Ochsner Clinic, and Alton Ochsner Medical Foundation, New Orleans, Louisiana

MY FELLOW MEMBERS of the Southern Surgical Association, to serve as your president is an honor I cherish. I know that in choosing me, it was not the intention of the council to praise an individual, but rather to reward a loyal member whose affection for the association is obvious and whose membership in the association is regarded as a privilege. I thank the council for this opportunity.

A majority of the founding members of the Southern Surgical Association (originally the Southern Surgical and Gynecological Association) served as medical officers in the Confederate Army. However, with the exception of two generic papers presented by Bedford Brown (one on the treatment of gangrenous wounds and the other on stab wounds of the peritoneum), in which he inclusively mentioned some of his experiences during the Civil War,[1,2] surprisingly, no papers on surgery during the Civil War have been presented at meetings of this association. The exact reasons for this are unknown; however, maybe they wished to forget that holocaustic experience, or they had no reason to recall their surgical experiences because little was accomplished. It is likely that both factors were contributory. To be able to forget the War Between the States would have been a blessing. To quote Lincoln,[3] "It was terrible to both the North and the South. It was terrible in its magnitude, in its persistence, in its ferocity, and in its cost of human life." More American lives were lost in the War Between the States than in all other conflicts in which our country has ever been engaged. If the population of our country at the time of the Civil War were compared with that of modern times, the loss would be even greater proportionally. An estimated 620,000 lives were lost: 360,000 Union soldiers and 258,000 Confederate soldiers. The chance of a soldier returning home was less than one in four.

Never has a period in American history aroused such interest, attested to by historians who have written more about the Civil War than about any other period. Americans have read more books about these 4 years than about all the rest of American history. More than 50,000 books have been published, and countless letters, diaries, novels, histories, memoirs, biographies, narratives, poems, scripts for stage and screen, and music have been written. Although most of the writings are devoted to heroism, sacrifice, and bravery, nearly an equal amount describe the anguish, squalor, and suffering. Having witnessed the horrors is ample reason for the early members of our association not to have desired recall for scientific publication. Family fought against family, friend against friend. Thousands of Southerners fought for the Union, and thousands of Northerners fought for the Confederacy. It was truly a war that divided not only states, but also families and friends. The tragedy of the war is probably best described by Allan Nevins in his book *The War for the Union*[4]:

> We have lost not only these men but their children and their children's children . . . we have lost the books they might have written, the scientific discoveries they might have made, the inventions they might have perfected. Such a loss defies measurement.

Conversely, medical advances are often spurred by wars. New concepts and improvement of surgical techniques and instrumentation have resulted; however, in the Civil War there were no discoveries and little was added to the existing medical knowledge. The state of the art and science of medicine was at a low ebb in 1860 at the beginning of the war. The discovery of Pasteur and associates and the techniques of Lister that completely

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revolutionized medical and surgical practice were unknown; hence, the live-saving management of wounds and the diagnosis and prevention of most diseases were denied the Civil War soldier. The problems and challenges of the doctors of the Confederate Army and Navy were astronomical. Only a few had experience in military medicine and surgery. Most had obtained training in the offices of old practitioners who served as preceptors. However, many of the younger doctors had attended medical schools that usually were connected with a college. Most of the established medical schools were in the North, and schools such as the University of Pennsylvania, Jefferson Medical College, Harvard School of Medicine, and University of New York attracted many Southern students. As the Southern population expanded, and as part of a move for Southern independence, medical schools were formed. The first such school was the Medical College of South Carolina located in Charleston in 1824, and by the time the first shot was fired on Fort Sumter, there were 21 medical schools in the Southern states.

On February 26, 1861, a provisional congress of the confederate states at Montgomery, Alabama, authorized the establishment of a medical department of the army. It provided for one surgeon general, four surgeons, and six assistant surgeons. The surgeon general was to have the rank of colonel, surgeons the rank of major, and assistant surgeons the rank of captain. Medical officers were given authority to exercise command only in their own departments.[5] President Jefferson Davis vetoed the bill, but as the war progressed, it became obvious that it was to be a long war, and he was empowered to appoint a provisional army of as many surgeons and assistant surgeons as deemed necessary. Not until April 1863 did he and the Congress realize the need for a medical department. He then appointed 10 medical inspectors charged with supervising hospital and camp sanitation and gave them full authority, allowing them to reorganize into a medical department. Eventually there were 18 surgeons serving as medical directors in the field and supervising the work of the medical officers. There were also eight medical directors of hospitals, six field medical inspectors, and seven medical inspectors of hospitals. Each command engaged in combat was to have one surgeon and two assistant surgeons. Ultimately, an estimated 3400 physicians served in the Confederate Medical Corps. The Union counterpart enrolled 11,700, or approximately one doctor for every 133 Northern soldiers, as compared with one doctor for every 324 Southern soldiers.[6]

The loyalty and fierce patriotism of the Southern doctors inspired most doctors to put aside their professional status and enroll as combat soldiers. Because the individual seceding Southern states and Confederacy did not have a medical department at the beginning of the war, more doctors saw combat duty in the South than in the North. It is estimated that the number of physicians who served as combat soldiers equalled the number who served in the medical department. Six physicians rose to the rank of general in the Confederate Army, all six serving as combat officers.[7] No physician attained the rank of general through the Confederate Medical Department. Although the Confederate Surgeon General, Samuel E. Moore, carried out his duties with the relative rank of a brigadier general, there is no report of his being conferred this rank by the Confederate legislature.[8]

The great task before the Confederate Medical Corps is illustrated by the fact that nearly 4,000,000 cases of disease or wounds were treated, which translates to every Confederate soldier having fallen victim to disease or wounds an average of six times during the war.[9] The doctor-to-soldier ratio was less than one half that of a modern army.[10] The Confederate Army was handicapped not only from the standpoint of manpower but also from the lack of drugs, pharmaceuticals, surgical instruments, supplies, food and even books. In antebellum years, drugs, instruments, and texts were all supplied by Northern cities.

The overall medical responsibility for a brigade or division was assumed by the surgeon. Once he learned from the commanding officer where the troops were to engage in battle, he chose the site for the field hospital, usually behind a natural obstacle for shielding from hostile fire. The assistant surgeon would be placed between the regiment and the field hospital. At the front, the assistant surgeon provided first aid, which consisted chiefly of controlling hemorrhage, splinting fractured limbs, and administering pain killers, which sometimes was morphine or opium, but more often was only brandy or whiskey. He would send the wounded from the front on stretchers or by ambulance to the field hospital. The rude ambulances were usually springless farm wagons that severely jolted the wounded as they were drawn by mules through uneven or wooded terrain or on roads badly rutted by artillery and supply trains. If able to undertake the journey, the wounded Southern soldier often preferred to walk to the field or regimental hospital than to go by ambulance, were any available.

Nearly 200,000 Confederate soldiers were wounded, of which 94,000 died in battle. The minié ball was responsible for 94% of the injuries; shells and canisters caused only 6%.[11] The minié ball (Fig. 1), a cylindro-conical rifle bullet named for its inventor, Captain Claude Etienne Minié of France, produced a vicious wound. Unlike the bullets of today, which are made of steel and travel at such high speeds that they pierce through the body with a nice neat hole, the minié ball with its relatively low velocity would tumble in its course through the body, dragging with it pieces of clothing and debris.

Wounds of the extremities accounted for almost 65% of all wounds; one half involved the upper extremity and

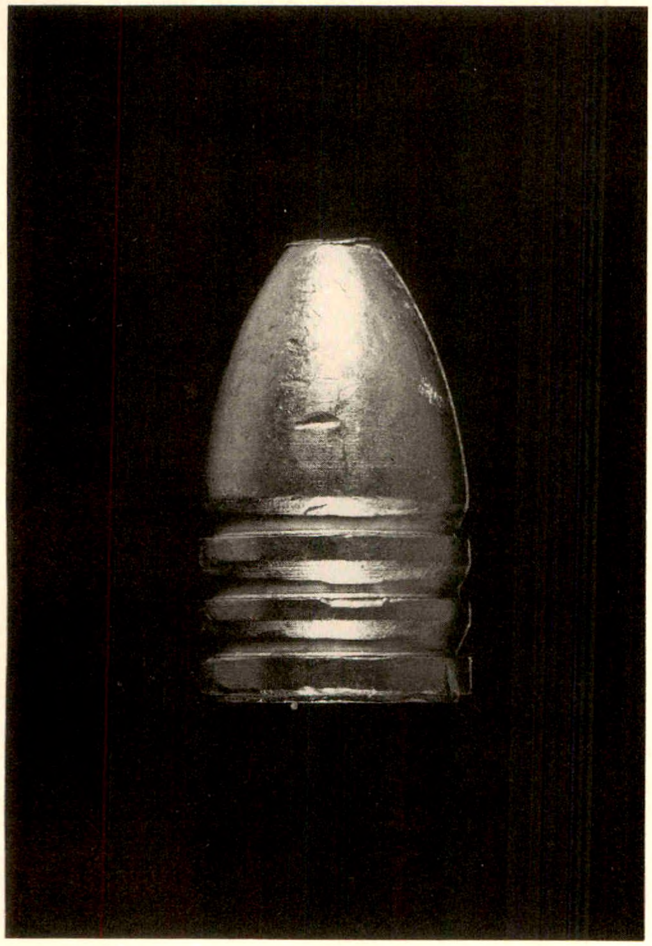

FIG. 1. Minié ball.

one half involved the lower. Confederate soldiers suffered 25,000 amputations from these wounds. Reports of deaths from amputations varied between 20% and 87%, with an average of 30%.[8,12] The mortality rate from delayed or secondary operation was double that of primary operation. Gunshot wounds of the abdomen, particularly those penetrating the viscera, were regarded as certainly fatal. Except when necessary to return viscera, no operation was attempted; all the surgeon could do was to administer opium and whiskey. Penetrating wounds of the chest were fatal in 62% of cases. Empyema was the primary complication and was treated by open drainage or insertion of drain tubes.[13] Whether the gaping chest wound should be hermetically sealed or left open was controversial.

Operations were performed on any available flat surface, usually a door laid across barrels or boxes. The anesthetic agent used by the Confederate medical officer was almost exclusively chloroform, which had an advantage over ether because of its small bulk, because it was noninflammable, and because of its speedy action. It was dropped on a sponge, handkerchief, or cotton cloth and given sparingly to preserve the supply. The patient was awake by completion of the operation. Because speed was the most important factor in survival, the patient obviously received very little anesthetic; hence the operative death rate was inordinately low (only one per 2000 operations). At a national medical meeting some years after the war, Dr. Hunter McGuire reported that chloroform had been administered in hospitals over 40,000 times under his supervision without a single death.[14] The supply of this important agent to the Confederate Medical Corps was greatly enhanced when, during the Winchester Battle in May of 1862, Stonewall Jackson's men captured Union supplies and made off with 15,000 cases of chloroform.

The ideal placement of the operating tables was in open air wherever the light was best, whether from the blazing sun or a silvery moon. During the vicious battles, the constant stream of amputations would proceed through the night, the surgeons operating by moonlight or lantern. The surgeon would stand with his sleeves rolled up, his apron smeared with blood, cleaning his knife on the sole of his boot or holding the knife in his teeth while his hands were otherwise occupied. Stories have recounted surgeons who would work hour after hour, and when unable to endure any longer, would break down and cry.

Experience from the Crimean War dictated that early amputation could lower the mortality rate from severe wounds of the extremity.[15] Chisholm, in his 1861 "Manual of Military Surgery for the Use of Surgeons in the Confederate States Army",[16] asserted that "All needful operations must be performed within 24 hours or the wounded would suffer from neglect." Many young doctors, anxious to become proficient in amputation, were overzealous in performing the operation; hence, it was not uncommon to see wounded men hide from the operating surgeons to save limbs condemned to amputation. This great propensity for chopping off limbs stimulated the Surgeon General in August 1863 to form a consultation board that had the power to approve every major operation if time allowed.

Surgeons were taught that extraction of the bullet foreign body was vital to the care of wounds. Simple and elegant bullet probes and extractors were developed. Porcelain probes were believed to distinguish lead bullets from tissue and other foreign bodies. Surgeons also were taught that the finger was the best probe; however, the searching finger with its contamination was often the cause of the patient's death.

Once the bullet was removed, steps were taken to control bleeding. The use of ligatures and the skill in their application was an advance in surgical technique learned by the Confederate surgeon. The ends of the ligature were customarily allowed to protrude from the open stump of the amputation. On the third or fourth postoperative day, when the ligated vessel necrosed, secondary hemorrhage frequently occurred. Three quarters of those who died in battle died as the result of hemorrhage, whether primary or secondary.

Many battles were fought far from a metropolitan area. Because the number of casualties was so great, available surgeons were few, and hospitals were nonexistent, the result was disastrous. For example, at Shiloh, a Confederate army of 44,699 suffered 8012 wounded, and there were no hospital facilities within 100 miles.

After the battle, the first order of business was to sort out those who could be saved from those who could not; for instance, a man shot in the head or spine was beyond help. Such wounded were merely placed in orderly rows and left to the resources of nature (Fig. 2). After many great battles, the battlefield as well as the roads to and from the battle site were lined with wounded in all stages of misery, groaning and crying and begging for water, whiskey, or food, and pleading for surgeons to come to their attention. Many were delirious, shouting out battle cries or calling for friends; some would even beg to be shot to escape their miserable condition.[11] The horror was compounded by the inadequacy of resources available to help them.

The Civil War surgeon lamentably knew nothing of the doctrine of sepsis and the proper use of antiseptics. Although antiseptic agents had been recognized in advance of the war, Lister's first article on antisepsis was not published until 1867, a couple of years after the war ended. The importance of sterilization or even rudimentary cleaning of instruments and wounds had not been established.[17]

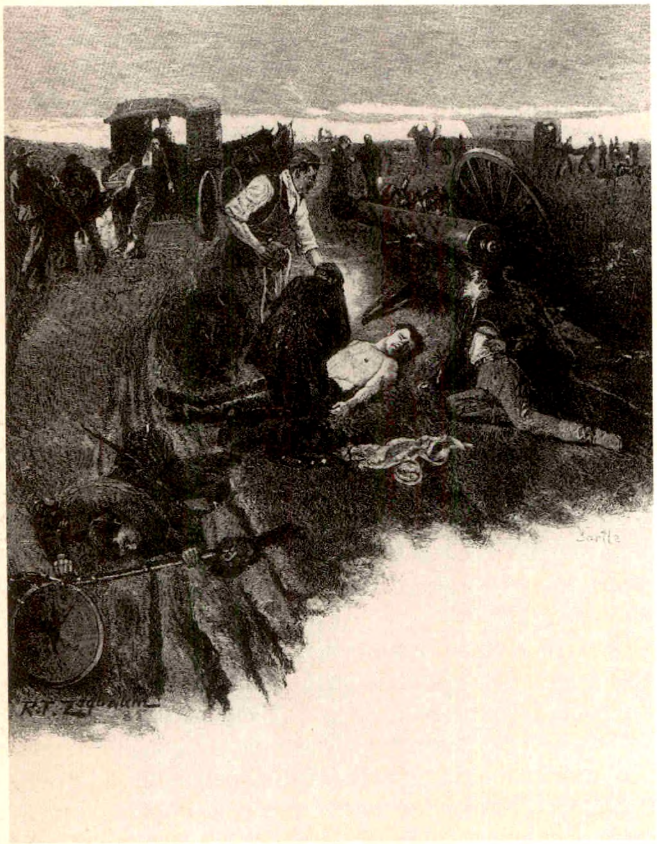

FIG. 2. Surgeon and triage of the wounded.

Physicians of that time theorized that healing from lost tissue was based on inflammatory reaction; therefore, the surgeon's aim was to promote suppuration in the form of a creamy pus, referred to as laudable pus, that appeared in wounds healing by secondary intention. The appearance of laudable pus on the third or fourth day was viewed with satisfaction, and in some locations after battle, the air was heavy and nauseating with its odor.[11] The Confederate surgeon did use disinfectants, such as the chlorides, carbolic acid, permanganate of potash, turpentine, and powdered charcoal, not for their antiseptic effect, but as deodorants to control the offensive odors.

Dressings for the wounds were obtained by diverse means. Cotton factories were the major source, and the women of the South furnished sheets, bedspreads, skirts, and other worn goods. When sponges became scarce, cotton rags were used, sometimes over and over again. The dressings and bandages that were passed from one patient to another were cleaned by boiling, which serendipitously produced a sterile dressing. Silks for ligatures were unavailable, but the Southern surgeons improvised, employing cotton or flax threads, and even horse-hair, which was boiled to render it soft and pliant, producing another accidental aseptic product.

Gangrene, tetanus, erysipelas, and pyemia, the so-called surgical fevers, were primarily responsible for the delayed deaths among the wounded. As mentioned, surgeons of the day believed in "a laudable pus" and were astonished when an occasional wound healed without it.[18] Hospital gangrene usually occurred in the lower extremities. The patients were in acute pain with cold sweats and had nauseous, putrefying wounds. Little was known of gangrene before the war. Hospital gangrene, as it was called, included a wide range of infections, a combination of aerobes and anaerobes, such as *Streptococcus* combined with anaerobe gram-negative bacteria. First appearing in June of 1862 and progressively increasing throughout the war,[11] hospital gangrene usually occurred in crowded camps and hospitals facilitated by extreme fatigue, depression, exposure to the elements, or insufficient food. The prevalence of the disorder is understandable, considering the lack of knowledge of antisepsis and the unsanitary conditions of the camps and hospitals. It is ironic that during the course of numerous detailed microscopic examinations of pus from gangrenous wounds, Dr. Joseph Jones saw the bacillus responsible for gangrene but dismissed any connection between the bacillus and the infection.[19] "Animalcules of simple origin and endowed with active rotary action abound in hospital gangrene." "The gangrenous matter," he postulated, "appeared to afford a nidus in which the simple forms of animal and even vegetable life are rapidly generated and multiplied." Jones' failure to connect the bacteria he observed with gangrene is easily understood considering that the miasmatic theory of disease, defined as "nocuous effluvium that emanated from the cold dark ground," was still firmly entrenched in America during the Civil War. The Confederate medical officer did his best to control the various surgical infections, and eventually a great premium was placed on cleanliness, proper ventilation, and a nutritious diet. The outbreak of gangrene caused some hospitals to be completely closed until they were thoroughly cleansed with disinfectants and whitewashed.

An inefficient induction system failed to reject the unfit and disease-prone from active service. Recruits were lucky to have received any semblance of a physical examination. Tales of women successfully enlisting as men testify to the inadequacy of initial screening. Recruits from rural districts, unlike those from cities, had not experienced communicable infantile diseases, and failure to include the available smallpox vaccine as a standard part of the induction procedure resulted in alarming outbreaks during campaigns.

Nearly 200,000 Confederate soldiers died from illness, three times more than from battle casualty. Armies were literally rendered inefficient or were destroyed, not so much by the actual fighting as by the steadfast action of disease. Because there was no knowledge of bacteriology and the relationship of bacteria to disease, there was an absence of preventive medicine. Most of the afflictions were attributed to the miasma. Thus, in the early portion of the war, hospital windows were left closed, pus was expected to collect in devitalized tissue, and contaminated dressings were passed from one patient to another when the previous owner either recovered or died.

The major diseases that affected the Civil War soldier were infectious. Typhoid or camp fever accounted for 28% of the deaths. The camp was more hazardous than the battlefield, and because more time was spent in camp than in combat, more deaths occurred from disease than from battle. Most camps were an accumulation of filth, the odor of which could be detected from great distances. It was not uncommon for two thirds of a field regiment to be on sick call.[20] Poor sanitation was the rule. Latrines were in close proximity to cooking areas. The importance of sewerage, garbage, animal offal, manure, and dead horse and mule disposal; of insect and rodent control; and of food and water protection and purification was largely unknown.

Shoes were scarce, and as tents became less available with the progression of the war, soldiers were exposed to adverse weather conditions. Food was inadequate, particularly in view of the extra physical demand of exhausting marches and combat action. Historians describe the soldiers as being cadaverously thin. As the war progressed, the diet of the Southern soldiers worsened. By the middle of the conflict, they made do with ant-infested corn meal and horse meat, but by the final days of the war, the troops were reduced to eating fried dog, boiled cat, and roasted wharf rats.[11]

Typhoid fever progressively diminished during the war, and chronic diarrhea and dysentery progressively increased. If typhoid was the great killer, dysentery and diarrhea was the great nuisance, affecting 78% of the soldiers annually. This bothersome and potentially life-threatening malady was called dysentery when tenesmus was accompanied by blood in the stool, or diarrhea if blood was not present.[21] Deaths from disease were fewer when the troops were campaigning or in battle than when they were in stationary encampments. Likewise, diarrhea and dysentery was less of a problem when the troops were on the move, because then the water supply was new almost every day and was less likely to have been contaminated by the men themselves. Privies in the camps were often established over water, thus polluting the water supply, a practice that was partially responsible for the morbidity and mortality rates from diarrhea and dysentery. Regulations eventually dictated that latrines were to be established at a distance, and men were compelled to use them under penalty. Because of the inconvenience of traveling to distant latrines, however, the soldiers, and in particular the "country boys," used the camp site. Also, penalties were rarely imposed.

The treatment of diarrhea and dysentery was varied and nonspecific and in many instances harmful. Some physicians popularized cauterization of the lower 6 inches of the rectal mucosa.

Malaria ranked second to diarrhea in producing disability. Although more prevalent among Southern troops, it was more fatal to the enemy, probably because of Southerners' previous experience with the disease.[18] The Confederate medical service used quinine as a prophylactic measure against malaria, but scarcity of the drug soon prohibited its use. Not infrequently, entire army departments were completely incapacitated. For example, in the Department of South Carolina, Georgia and Florida, with a strength of approximately 75,000 men, 41,000 cases of malaria were reported between July 1862 and July 1863. In other areas, as many as 80% of personnel were afflicted at one time.[22]

A myriad of contagious and noncontagious diseases were encountered, such as streptococcal infections (especially a wound infection), typhus, pneumonia, diphtheria, smallpox, tuberculosis, and "rheumatism," a term used for any joint or extremity pain.

One of the tragic aspects of Confederate medicine was that most of the deaths would have been entirely preventable or curable by present-day knowledge and facilities. Soldiers died of conditions over which the Confederate medical officer had no control. They died because of exposure; because of inadequate food; because of lack of clothing, tents, blankets, medicine, and drugs; but mostly they died because of the lack of knowledge of the cause of illness and the proper management of wounds. Only in the North were drugs produced, and the blockade effectively prevented all drugs from getting to the South. The "Trading with the Enemy Act" of 1865, enacted by the Union, essentially prevented the South from obtaining drugs and equipment. Some of the doctors in the North suggested that medicinal agents be removed from the contraband list; however, when the proposal was presented to groups such as the American Medical Association, most of the doctors heckled and hissed. At the onset, the South had no pharmaceutical plants, and as a result, the Surgeon General ordered the establishment of facilities in Mobile, Charleston, Columbia, and Augusta. Although some drugs were manufactured, such as alcohol, silver nitrate, potassium, iodine, and ether, supplies were limited and many other kinds were needed. Opium, morphine, and quinine had to be smuggled in.

Indigenous substitutes became the hallmark of Confederate medicine. Surgeon General Moore commissioned Dr. Francis P. Porcher to publish a book entitled *Resources of the Southern Fields and Forest* as a help for obtaining local drugs unable to be secured because of the blockade.[23] Cucumbers were used for burns, pokeweed for camp itch, geraniums for diarrhea, persimmons for dysentery, and charcoal for diphtheria. A tincture of a compound of willow, dogwood, and yellow bark, appropriately called "old indigenous," was used as a substitute for quinine. Efforts were made to cultivate the poppy in Florida and North Carolina, whose unique seed capsules yield a gum with an effect not unlike Turkish opium.[24] Union hospitals were able to get all the drugs they wanted. Private firms, which have remained as giants in the pharmaceutical world today, included Edward E. Squibb, John Wyeth, McKesson & Robbins, and Charles Pfizer and Company.

Added to the problems encountered by the Confederate surgeon in practicing medicine was the low status of the doctor compared with field officers. The legal position of medical officers was poorly defined, and regimental surgeons were directly subordinate to field colonels. Moreover, when medical supplies, personnel, and transportation services were inadequate, which was the usual, surgeons had no control over procurement.

Battlefield promotions and other rewards were won by the fighting men; however, regardless of their risks and work, the field surgeons would receive no more than a passing notice. The death rate among Confederate doctors, both from enemy action and from disease, was higher than that of any other staff corps. Statues of generals are in every town, and every village has its statue to a private soldier, but no state or national monument is dedicated to the Confederate surgeon. At Gettysburg, every battery site is marked with a recording tablet; every general who died is remembered in bronze or marble; but not a single notice of the surgeons who died can be found.[25]

The only individual to be executed for alleged war crimes during the Civil War was a doctor. A doctor by preceptorship, employed on Marshall Plantation at Milliken Bend, Louisiana, immediately before the war, Henry Wirz was commander of the prison at Andersonville, Georgia. During the Civil War, prisons were factories for disease and death, both in the South and the North.[26] Grant stopped the practice of exchanging wounded prisoners in 1864 to increase the burden on Lee's limited resources.[27] After the war, the Adjutant General of the US Army reported that 19,600 Confederates died in Union prisons and 26,168 Federals died in Confederate prison.[11] Undoubtedly, the conditions at Andersonville Prison were deplorable. The stockade was overcrowded. With a capacity for fewer than 10,000 prisoners, the number imprisoned grew to over 33,000, for an average space of only 36 square feet per prisoner.[28] Thus, even basic sanitary conditions could not be obtained. The decision to prosecute Dr. Wirz for the horrors of Andersonville placed Dr. Joseph Jones in an uncomfortable position, for he feared that the research he had done among the Union soldiers at Andersonville would be construed as documented evidence of Confederate atrocities. He stated, "The report of the Federal prisoners at Andersonville should never see the light of day, because it was prepared solely for the eyes of the Surgeon General of the Confederate States Army; and the frank manner in which the subject had been discussed would only engender angry feelings and place weapons in the hands of the victors." His worst fears materialized. Without any warning, Dr. Jones was ordered to report to Washington to Colonel Norton P. Chipman, Judge Advocate and Prosecuting Attorney in Captain Wirz's case, as a witness in the trial and to take with him all papers, reports, and recordings pertaining to the Andersonville Prison. At the trial of Captain Wirz, when Jones was questioned, he was surprised and dismayed that his 600-page report had been reduced to a mere 20 pages and that the material containing explanation for the dreadful conditions at Andersonville had been left out.[29] He considered the abstract to be a most unfair and garbled statement. Although in the opinion of Dr. Jones and many others Dr. Wirz did the best he could with what the Confederacy provided, the aroused postwar attitudes of many victorious Northerners demanded that the rebellious South be punished. Neither Jefferson Davis nor Robert E. Lee nor any other well-known Southerner, however, was formally charged with war crimes. Instead, in a true 19th century witch hunt, Captain Henry Wirz, the Commandant of Andersonville Prison, became the sacrifice. Dr. Wirz was hanged on November 10, 1865 (Fig. 3).

After the war, the desperate economic environment in the South naturally affected the medical profession. In the immediate postwar period, Southern surgeons were not held in high esteem by surgeons of the North and abroad, and to arise from that position required great effort and fortitude.

Many notable surgeons served the Confederacy honorably and excelled after the war as physicians, educators, scholars, or politicians. As proof that the Confederate Medical Corps included many able and promising members of the medical profession, almost 100 Confederate medical officers were included in the authoritative medical biographical work, *American Medical Biographies.* To pay tribute to these 100 is beyond the bounds of reason; however, I would like to highlight two of the founding members of our association who excelled as surgeons both during and after the war.

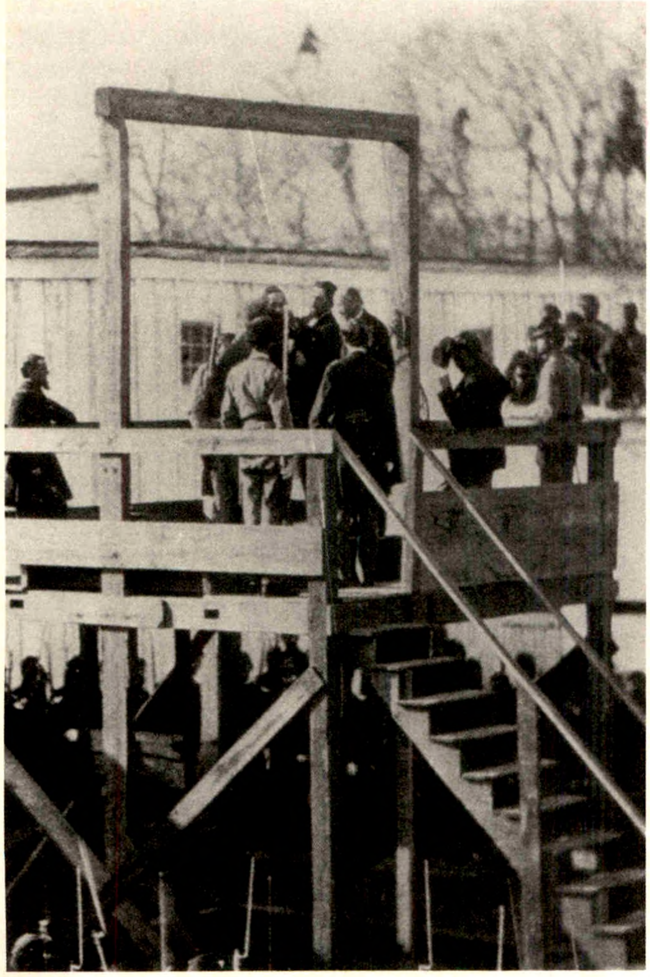

FIG. 3. The hanging of Captain Henry Wirz.

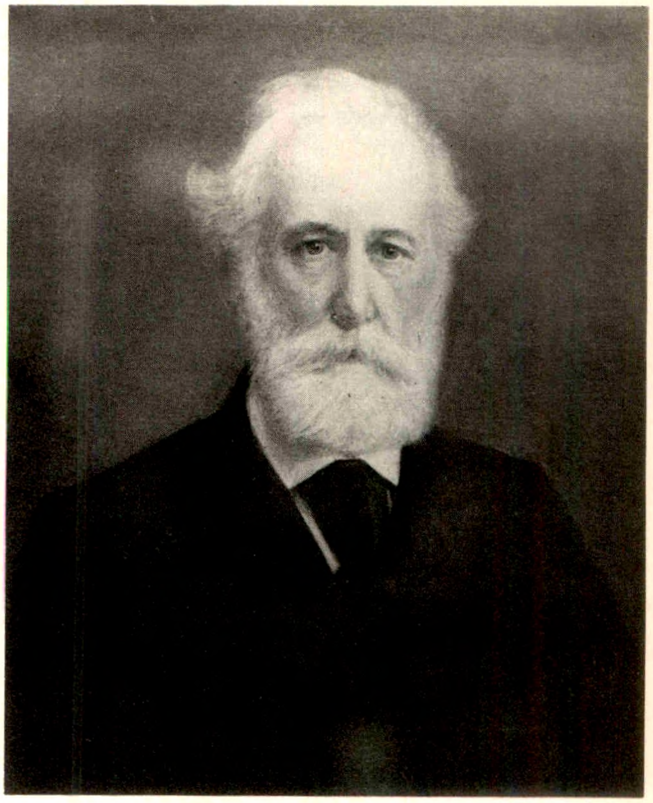

FIG. 4. Robert Alexander Kinloch.

Robert Kinloch

Robert Alexander Kinloch (Fig. 4) was born in Charleston, South Carolina, on February 20, 1826. He graduated from the College of Charleston with distinction. He received his medical degree from the University of Pennsylvania and spent 2 years in the hospitals of Paris, London, and Edinburgh. Returning home, he began to practice in his native city when the war began. He was among the very first surgeons to receive a commission and was on duty at the first battle of Manassas. His military career was exceptional in that he served at various times on the staffs of Generals Lee, Pemberton, and Beauregard. Also, he was a member of the Medical Examining Board at Norfolk, Richmond, and Charleston and subsequently held the position of Medical Inspector of Hospitals for South Carolina, Georgia, and Florida. He was known as an innovative surgeon, having saved lives of soldiers not expected to survive. After the war, he practiced in Charleston, South Carolina, and was soon elected Chief of Surgery at Roper Hospital. In 1866, he was elected to the Chair of Materia Medica in the Medical College of the State of South Carolina with the understanding that he would transfer to the Chair of Surgery when the position became vacant. This agreement was fulfilled, and in 1869 he was transferred to the Chair of the Principles and Practice of Surgery and subsequently to that of Clinical Surgery, which he occupied until the time of his death. In 1888, he was elected Dean of the faculty and continued to serve in this capacity also until he died. He was President of the Medical Society of South Carolina, President of the South Carolina Medical Association, and a founder of the American Surgical Association, serving as a member of its council. He was also active in the American Medical Association and was First Vice President in 1884. For a short time, he was editor of the Charleston Medical Journal.

Dr. Kinloch was considered a very able surgeon, bold and determined, possessing a rare skill in execution and perfect poise in the face of unforeseen emergencies. He was the first surgeon in America to successfully resect a knee joint for chronic disease, the first to treat fractures of the lower jaw and other bones by wiring the fragments, and the first to perform an exploratory laparotomy for gunshot wounds of the abdomen.[30] He was original in his thinking and demonstrated a modern viewpoint that was not universal. He defended Listerism when most of his colleagues were attacking its principle. As a professor and as Dean, he worked diligently to elevate the standards of medical education and was annoyed when restrictions beyond his control hindered action. He stated, "The standards of the college could and should be elevated. It is painful to me to say that I am powerless to improve the situation."[31] He was a man of strong convictions, rejecting the impractical but always acting professionally. In controversy he wielded a caustic pen and did not spare his adversary. Kinloch was by far the most prominent surgeon in his section of the South.[32]

Dr. Kinloch suffered from heart disease for many years and died of pneumonia on December 23, 1891.

Hunter Holmes McGuire

Hunter Holmes McGuire (Fig. 5) was born on October 11, 1835, in Winchester, Virginia, a town that changed hands approximately 80 times during the Civil War. His father, Hugh Holmes McGuire, was a prominent physician and surgeon who founded Winchester Medical College, the first medical college in the state of Virginia, from which Hunter McGuire received the first of two medical degrees. Afterward, Dr. McGuire traveled to Philadelphia, where he attended courses at Jefferson Medical College and at the University of Pennsylvania. He joined Drs. Luckett and Pancoast as teachers of a highly successful quiz course. Dr. McGuire was a superb teacher, and many Southern students in Philadelphia accepted him as their spokesman. The hanging of John Brown for his actions at Harper's Ferry led to conflict between Northern sympathizers and Southern medical students residing in Philadelphia. Because of the tension, the Southern students wished to transfer to a Southern school of medicine. As their leader, Hunter McGuire was successful in transferring all the students to the Medical College of Virginia without a loss of credit. He apparently paid from his own pocket the train fare of the entire group (there were over 300 medical students). One hundred forty of these students attended the Medical College of Virginia, and the others transferred to other Southern schools. Along with the students from Philadelphia, Hunter McGuire matriculated in the Medical College of Virginia, where he received his second medical degree.

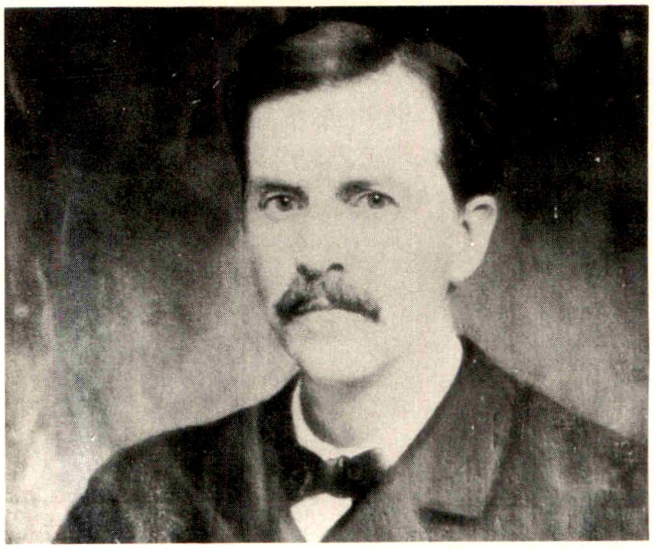

FIG. 5. Hunter Holmes McGuire.

When Virginia seceded from the Union, he volunteered and was mustered in as a private in the 2nd Virginia Regiment. He was soon commissioned a surgeon and appointed Medical Director of the Army of the Shenandoah under the command of General Stonewall Jackson. He continued to serve as Chief Surgeon of Jackson's command until the death of that great soldier. In May of 1862 at the battle of Winchester, Virginia, McGuire (who considered military surgeons to be noncombatants) persuaded General Jackson to release seven Union surgeons who had been captured. Under the agreement, these surgeons would do their best to influence the United States government to release Confederate medical officers as well. A few weeks later, all medical officers who had been confined by both parties as prisoners of war were released and returned to their respective commands. Although the plan of exchanging medical officers as noncombatants was eventually interrupted by some disagreement between the Commissioners for Exchange, Dr. McGuire continued to release surgeons whenever it was in his power. His practice of liberating medical prisoners worked to his advantage. When he was captured at Waynesboro by Sherman's army, Sherman, on learning of McGuire's identity and knowing of McGuire's release of medical officers, some of whom were from Sherman's own command, ordered McGuire's immediate release.[33]

When General Jackson was wounded in the left upper extremity and right hand after achieving his greatest victory at Chancellorville, McGuire inherited the sad duty of amputating his left arm. Although General Jackson did well for the first 5 postoperative days, with primary healing of his wound except for the bone, where healthy granulation appeared, Jackson developed pneumonia that proved fatal on the 8th postoperative day.

After the war, McGuire returned to Richmond and was immediately successful. Some of his competitors thought he was capitalizing on his wartime fame and questioned the manner in which he had treated the South's most famous casualty. To exonerate himself of any charges of faulty judgment, Dr. McGuire published a report of Stonewall Jackson's injury and demise. His case was presented in such an interesting and authentic manner that never again was the treatment of General Jackson questioned.[34]

In 1866, Dr. McGuire was elected Professor of Surgery at the Medical College of Virginia, a position he held until 1878, when he became Professor Emeritus. In 1883, he organized the St. Luke Home for the Sick with a nurses' training school.

He had a huge medical practice, but he never turned away any old soldier who had worn the gray. Consequently, many did come to him with their illnesses and were treated without charge. Other patients would wait, business would wait, and even operations would wait, while no one dared interrupt his conversation with an old soldier as they reminisced.

Foreseeing the need for an extended and revised medical curriculum, Hunter McGuire founded the first 3-year medical school in the South, the University College of Medicine (Fig. 6), holding its presidency until the time of his death on September 19, 1890. After existing for 20 years, the University College of Medicine consolidated with Memorial Hospital and the Medical College of Virginia under the name of the latter.

Dr. McGuire was a bold, rapid, and dexterous surgeon. He knew when to operate, and better still, when to stop operating. He was the first to perform a suprapubic cystostomy for the formation of an artificial urethra in prostatic obstruction, an operation that, as the preferred operation of the time, relieving a terrible human suffering, earned him worldwide fame. As a teacher, he was fluent, lucid, and impressive (Fig. 7). As an author, he contributed regionally and nationally to many aspects of the practice of surgery.

Hunter McGuire had the rare distinction of having been elected president of every medical professional society in which he held membership, including the Medical Society of Virginia, the Association of Medical Colleges of the Army and Navy of the Confederate States, the American Medical Association, and the American Surgical Association, and he was the second president of our own Southern Surgical Association. He was granted honorary degrees from the University of North Carolina and from the Jefferson Medical College in Philadelphia. In his Presidential Address to the Southern Surgical Association, he ended the address with the following statement[35]:

> Gentlemen of the Southern Association, let our motto be lofty aim and united action. As southern men, let us show to the world

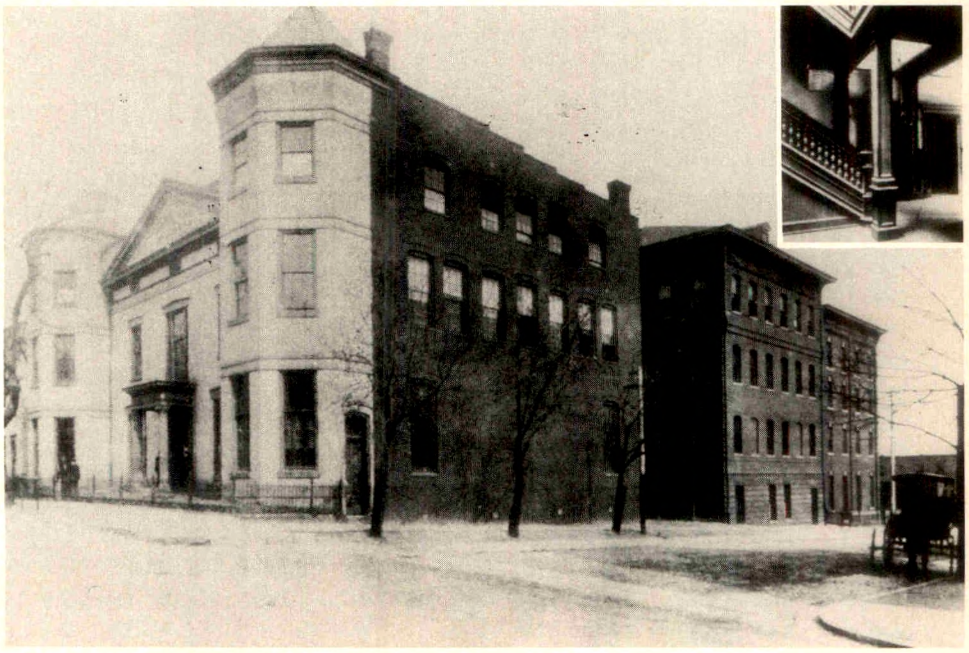

FIG. 6. University College of Medicine, circa 1895, founded by Hunter Holmes McGuire.

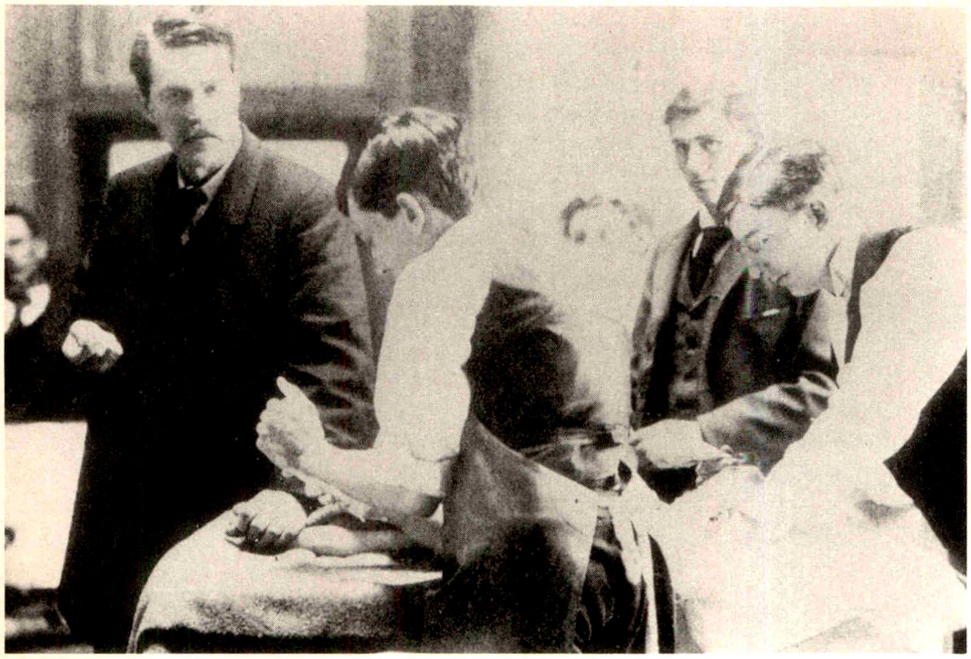

FIG. 7. Hunter McGuire teaching students. The student to whom he is speaking is his son, Stuart McGuire.

> that under changed conditions we have still the stamina of our forefathers. As members of our beloved profession, let us strive to be the first in scientific attainment, first in integrity, first in high purpose for the good of mankind.

Hunter McGuire probably did more than any to elevate the perceived postwar substandard status of the Southern surgeon to its present-day place of honor.

Dr. McGuire had a cerebrovascular accident, and after 6 months of a distressing illness, death came as a merciful relief on September 19, 1900.

Historians have argued whether the real reason for the Civil War was economic rivalry between the North and the South rather than slavery. It stands to reason that both are accurate because slavery, although an unacceptable inhumane practice, placed the South at an economic advantage. It is of interest that Lincoln did nothing to abolish slavery until nearly 2 years after the war had begun. The Emancipation Proclamation on September 22, 1862 stated, "On the first day of 1863, anyone holding slaves will be in rebellion against the United States of America." If the Southern surgeon was handicapped after the war, a freed slave had an almost impossible task.

Robert Fulton Boyd

Robert Fulton Boyd (Fig. 8) was born of slave parents in Pulaski, Tennessee, in 1858. He was educated in public schools in Pulaski. To continue his education, he worked half the day for his board while attending school the other half of the day and at night. He attended Fisk University and received his undergraduate degree from Central Tennessee College, after which he received an M.D. from Meharry Medical College in 1882 and a D.D.S., also from Meharry, in 1887. While attending college, he taught in the public schools and became principal of the public school for blacks in Pulaski.

Dr. Boyd was the first black man to venture into practice in Nashville. To further his education, he did postgraduate study at the University of Michigan and the Postgraduate Medical School of Chicago. He returned and became an assistant to Dr. Paul Eve. (Incidentally, Dr. Eve was the first to set up a medical board for the induction of physicians into the Confederate Army.)

He joined the faculty of Meharry, and during his career he chaired the Departments of Anatomy, Physiology, Hygiene, Chemistry, Medicine, Gynecology, and General Surgery.[36] In 1900, he established the 33-bed Mercy Hospital. When the building was destroyed by fire, he opened the Boyd Infirmary (Fig. 9), which served as the primary site for clinical training of Meharry students and was a major factor in the approval of the curriculum by the Flexner Committee and in the ultimate survival of the institution. Other black medical schools, with the exception of Howard University, were unable to meet the criteria for approval.

Dr. Boyd proposed the organization of a teaching hospital for Meharry and suggested that the hospital be named in honor of its first president, George W. Hubbard. In 1910, the Hubbard Hospital was opened and has grown to a modern 400-bed institution.

Dr. Boyd was one of the founders of the National Medical Association and was its first president. He was a respected teacher, acknowledged by most black surgeons of the time as their national leader. He was always affable, farsighted, and a friend of younger men, and he bristled

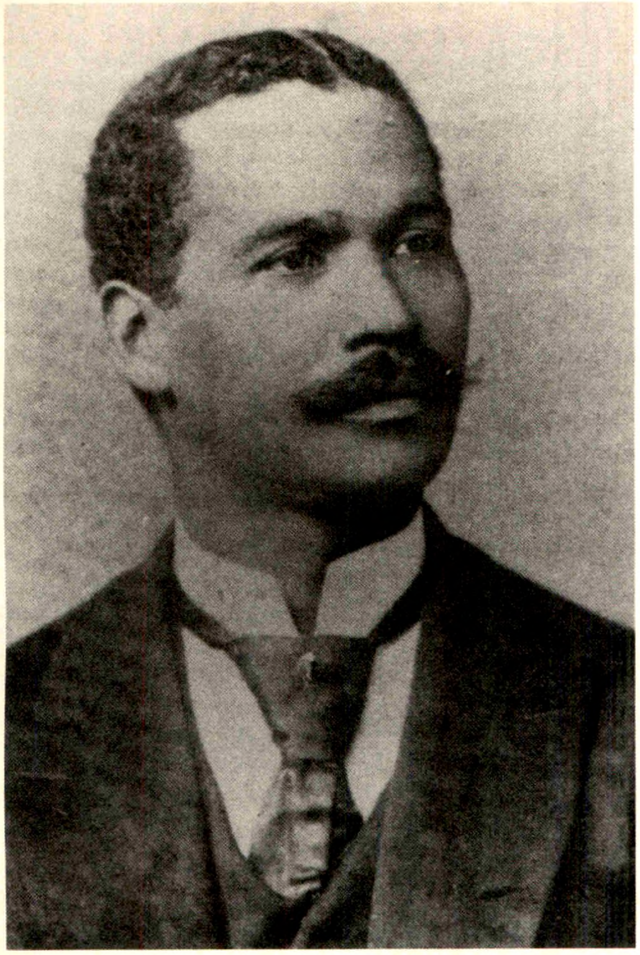

FIG. 8. Robert Fulton Boyd.

with energy. His life outside his profession was equally intensive. He served as president of the Peoples Savings Bank and Trust Company in Nashville, the first black trust company in the country. As a public-spirited citizen, he was always on the firing line of anything that would help his race and community. He even ran for mayor of Nashville. Unfortunately, the brilliant career of Dr. Robert Fulton Boyd ended prematurely at the age of 54, from what was thought to be acute indigestion, but was probably a myocardial infarction.

As mentioned earlier, Confederate surgeons were not credited with many accomplishments; however, they toiled valiantly for the cause in which they believed. Through their efforts during the war, from certain lessons they learned, indispensable developments were stimulated:

(1) Surgical dexterity: Their experience in handling the knife and the saw and the application of surgical ligatures led to the establishment of standard surgical maneuvers.
(2) Surgical initiative: Surgeons became less squeamish about entering previously forbidden areas such as the abdomen, chest, and cranial vault.
(3) Public health: Surgeons realized that cleanliness was associated with good results and that bad water, bad sanitation, and bad food led to misery and disease.
(4) Anesthesia: Its general usefulness was demonstrated beyond doubt through hundreds of thousands of administrations of chloroform and ether.
(5) Mobile hospitals: These hospitals were first used during the Civil War; they were the forerunner of

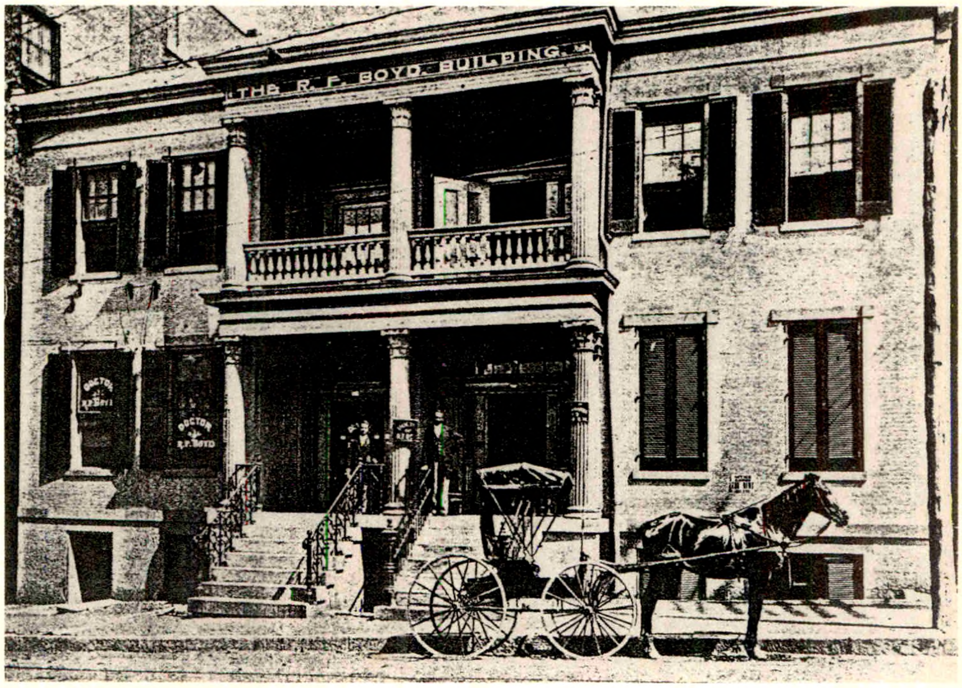

FIG. 9. Boyd Infirmary, which served as a clinical institution for Meharry Medical College.

the highly sophisticated mobile units used in recent wars.

(6) Dentistry: The Confederate army was the first to establish a dental service and to demonstrate the effectiveness of surgical exploration of the oral cavity, which eventually led to the formation of American dentistry.

(7) Nursing: Good nursing was found to be as important as proper medical attention, and it appeared that some of the best nurses were women.

(8) Orthopedics: Orthopedics was tremendously stimulated by the development of numerous innovative practical splints and workable artificial limbs.

(9) Rehabilitation: The multitude of amputees necessitated the development of rehabilitation.

(10) Medical Documentation: For the first time, medical and surgical successes and failures were systematically reported and analyzed. Never before had postmortem examinations been performed and recorded on such a large scale.

The South's most proliferative collector of medical history and data was Dr. Joseph Jones, who was guilty of romanticizing the conflict according to some sources, but who nevertheless described what I consider the genuine Southern surgeon[37]:

> The medical practitioners of the South gave their lives and fortunes to the country, without any prospect of military or political fame or preferment. They searched the fields and the forest for remedies; they improvised surgical implements from the common instruments of everyday life; they marched with the armies; and watched by day and night in the trenches. The Southern surgeon rescued the wounded on the battlefield, binding up the wounds, and preserving the shattered limbs of their countrymen: the Southern surgeons through four long years opposed their skill and untiring energies to the ravages of war and pestilence. At all times and under all circumstances, in the rain and sunshine, in the cold winter and burning heat of summer, and the roar of battle, the hissing of bullets and the shriek and crash of shell, the brave hearts, cool heads and strong arms of Southern surgeons were employed but for one purpose—the preservation of the health and lives and the limbs of their countrymen. The Southern surgeons were the first to succor the wounded and the sick, and their ears recorded the last words of love and affection for country and kindred, and their hands closed the eyes of the dying Confederate soldiers. It is but just and right that a Roll of Honor should be formed of this band of medical heroes.

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Protecting the Ischemic Spinal Cord During Aortic Clamping

The Influence of Anesthetics and Hypothermia

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Infrarenal circumaortic occlusion devices were operatively placed in 74 New Zealand white rabbits. Two days after operation the animals were randomly assigned to one of seven treatment groups: I, control, n = 23; II, halothane, n = 8; III, thiopental, n = 12; IV, ketamine (30 mg/kg intravenously), n = 6; V, halothane + hypothermia, n = 8; VI, thiopental + hypothermia, n = 12; VII, ketamine + hypothermia, n = 5. In each group, the infrarenal aorta was occluded for 21 minutes. Final neurologic recovery after restitution of blood flow was graded as acute paraplegia, delayed paraplegia (neurologic deficit developing after initial recovery), or normal. Halothane alone was of no benefit. Hypothermia with any anesthetic was completely protective and reduced neurologic deficits to 0% compared with 91% in controls ($p < 0.05$). Thiopental and ketamine treatment each reduced acute paraplegia to 17% (as compared with 61% in controls) and increased delayed paraplegia from 30% in controls to 75% and 50%, respectively ($p < 0.05$ for thiopental, $p = 0.10$ for ketamine). The authors interpret the increase in delayed deficits and decrease in acute deficits as being the result of partial spinal cord protection. These findings document that this model of spinal cord ischemia is sufficiently sensitive to identify interventional treatments that protect the ischemic spinal cord.

PARAPLEGIA COMPLICATES REPAIR of thoracoabdominal aortic aneurysms in 5% to 30% of patients, depending on extent of aorta replaced.[1,2] This complication is caused by spinal cord ischemia secondary to aortic clamping. A small fraction of patients awaken from anesthesia neurologically normal only to develop delayed-onset paraplegia 1 to 5 days later. The pathophysiology of delayed-onset deficits had previously been unknown, although postoperative hypotension or thrombosis of intercostal arteries had been suggested as possible causes. It has been our belief that delayed-onset paraplegia is a result of "borderline" ischemia, wherein the initial ischemic event was enough to induce some subclinical neuronal injury (initiating a deleterious metabolic cascade), yet not so severe as to result in acute paraplegia. We have previously suggested,[3-4] as have others,[5-13] that spinal cord edema within the confines of the spinal canal, cytotoxic activity of both direct and complement-activated leukocytes or microglia, oxygen-derived free radical injury, and vasoconstriction secondary to metabolites of arachidonic acid all may play a role in this metabolic cascade after sublethal spinal cord ischemia. Adjunctive therapeutic modalities would appear to be most likely to be effective in improving clinical outcomes in those patients who have such borderline ischemia.

Many animal models traditionally used to study paraplegia have failed to reliably produce delayed-onset neurologic deficits. We and others have previously demonstrated that aortic occlusion in the awake rabbit can cause varying degrees of spinal cord ischemia.[4,14,15] Using infrarenal aortic occlusion times of 20 to 21 minutes, one can expect a group of rabbits to exhibit a reproducible incidence of acute paraplegia in some and delayed-onset paraplegia in others. This model would appear to be an excellent tool to study therapeutic interventions directed at protecting the ischemic spinal cord.

We performed this study to determine if cooling and various anesthetic agents might be protective to the ischemic spinal cord.

Materials and Methods

Seventy-four New Zealand white rabbits (2.3 ± 0.02 kg) were given subcutaneous atropine (0.005 mg/kg) and anesthetized with intravenous xylazine (3 mg/kg) and ketamine (40 mg/kg). Intraoperative fractional doses of anesthetics were used to maintain appropriate levels of

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anesthesia. Animals were allowed to breathe room air without mechanical ventilation or tracheal intubation. Fur was clipped from the left flank, and the skin was prepared with povidone iodine. A vertical flank incision was made, and the infrarenal aorta was exposed through a retroperitoneal approach. A snare fashioned from PE-60 tubing and a 5-mm button were passed around the aorta immediately distal to the renal arteries. An 18-Fr. catheter was placed over the PE-60 tubing to facilitate later occlusion of the aorta (Fig. 1). The snare then was tunneled into a subcutaneous pouch on the anterolateral abdomen, where a small skin incision was made for later access. The wound was closed in layers, and a single suture was placed in the skin incision overlying the subcutaneous pouch (Fig. 2).

Forty-eight hours after recovery from anesthesia, animals were randomized into seven treatment groups (Table 1). Animals treated with ketamine (30 mg/kg) or thiopental (25 mg/kg) alone were given a single dose of the drug 3 minutes before aortic occlusion. In animals treated with hypothermia, however, one of the anesthetics, either halothane, ketamine, or thiopental, was administered so as to allow submersion of the animal in an iced bath until rectal temperature reached 30 C.

Infrarenal aortic occlusion was accomplished by removal of the skin stitch overlying the subcutaneous pouch and retrieval of the snare tubing. Snares were tightened for a total of 21 minutes. In control animals, two leads of a neurosensory stimulation unit were attached by clips to the hind limb of the animals and stimulated every 5 seconds with the lowest voltage required to assess motor and sensory function. The times of motor and sensory loss were recorded.

After 21 minutes of occlusion, the 18-Fr. catheter sleeve was removed and the PE-60 tubing was cut flush to the skin and allowed to retract subcutaneously. Animals were observed for neurologic recovery and graded as either dense paraplegia, paraparesis, or normal.

Animals were killed either at the time acute permanent paraplegia developed or after 5 days after clamping. Before death, animals were anesthetized with ether and the spinal column was exposed. Animals were killed with an intracardiac injection of saturated potassium chloride, and the spinal cord (proximal and distal to the level of aortic occlusion) was removed for fixation in formalin. The abdominal aorta and lumbar arteries were examined for the presence of any thrombus formation.

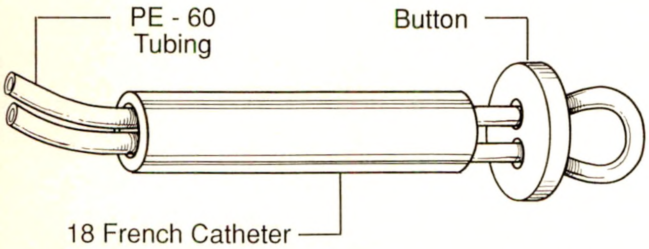

FIG. 1. Diagram of snare used to provide aortic occlusion.

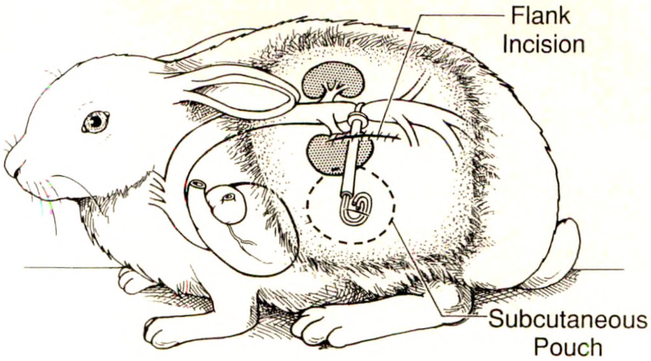

FIG. 2. Diagram of operatively placed snare retained in a subcutaneous tunnel.

Data were subjected to statistical analysis using the two-sided Fisher's exact test and Pearson chi square.

Animal care and disposal conformed to guidelines specified in the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 86-23, revised 1985).

Results

Weights of animals did not differ significantly between the seven groups. Within the control group (group I), the period after aortic clamping needed to cause loss of motor function (35 ± 3 seconds) was significantly less than for loss of sensory function (62 ± 3 seconds) ($p < 0.05$). This reconfirms an observation we previously reported regarding spinal cord ischemia in this animal model.[4]

There was no evidence of aortic or lumbar artery thrombosis identified in any animal.

Final neurologic outcome is represented in Table 2. Halothane treatment did not significantly change the risk of acute or delayed-onset paraplegia compared with controls. Both thiopental and ketamine treatment reduced acute paraplegia to 17% as compared with 61% in controls,

TABLE 1. *Treatment Modalities Used in Each Group*

Group	n	Treatment Modality
I	23	Controls
II	8	Halothane
III	12	Thiopental
IV	6	Ketamine
V	8	Halothane + hypothermia
VI	12	Thiopental + hypothermia
VII	5	Ketamine + hypothermia

TABLE 2. *Neurologic Outcome*

Group	Treatment Modality	n	Normal	Delayed-onset Paraplegia	Acute-onset Paraplegia
I	Controls	23	2	7	14
II	Halothane	8	0	1	7
III	Thiopental	12*	1	9	2
IV	Ketamine	6	2	3	1
V	Halothane + hypothermia	8*	8	0	0
VI	Thiopental + hypothermia	12*	12	0	0
VII	Ketamine + hypothermia	5*	5	0	0

* $p < 0.05$ *vs.* controls.

and increased delayed paraplegia from 30% in controls to 75% with thiopental treatment and 50% with ketamine treatment ($p < 0.05$ for thiopental, $p = 0.10$ for ketamine). Hypothermia to 30 C provided complete protection to the spinal cord, in that no acute or delayed neurologic deficits occurred.

Histologic features in the ischemic segment of spinal cords can be categorized into three general findings that correlate with neurologic outcome. Normal animals had ganglion cells in anterior horns, which were indistinguishable from those in nonischemic zones of the cord. Many animals with delayed-onset paraplegia had an intermediate degree of ganglion cell destruction with hyperchromatic nuclei and adjacent normal appearing ganglion cells. Rabbits with acute permanent paraplegia characteristically had total destruction of anterior horn cells with pronounced vacuolization (Figs. 3 through 5).

Discussion

Repair of thoracoabdominal aortic aneurysms requires cross-clamping of the thoracic aorta with complete interruption of aortic blood flow through the segment of the aorta involved by the aneurysm. These operations are associated with risks to multiple organs, although spinal cord ischemia with paraplegia is perhaps most devastating, especially psychologically. The cause of spinal cord injury with thoracic aortic cross-clamping is related to spinal cord ischemia, because critical intercostal arteries supplying the anterior spinal artery may be occluded. The incidence of spinal cord injury relates to the extent of the

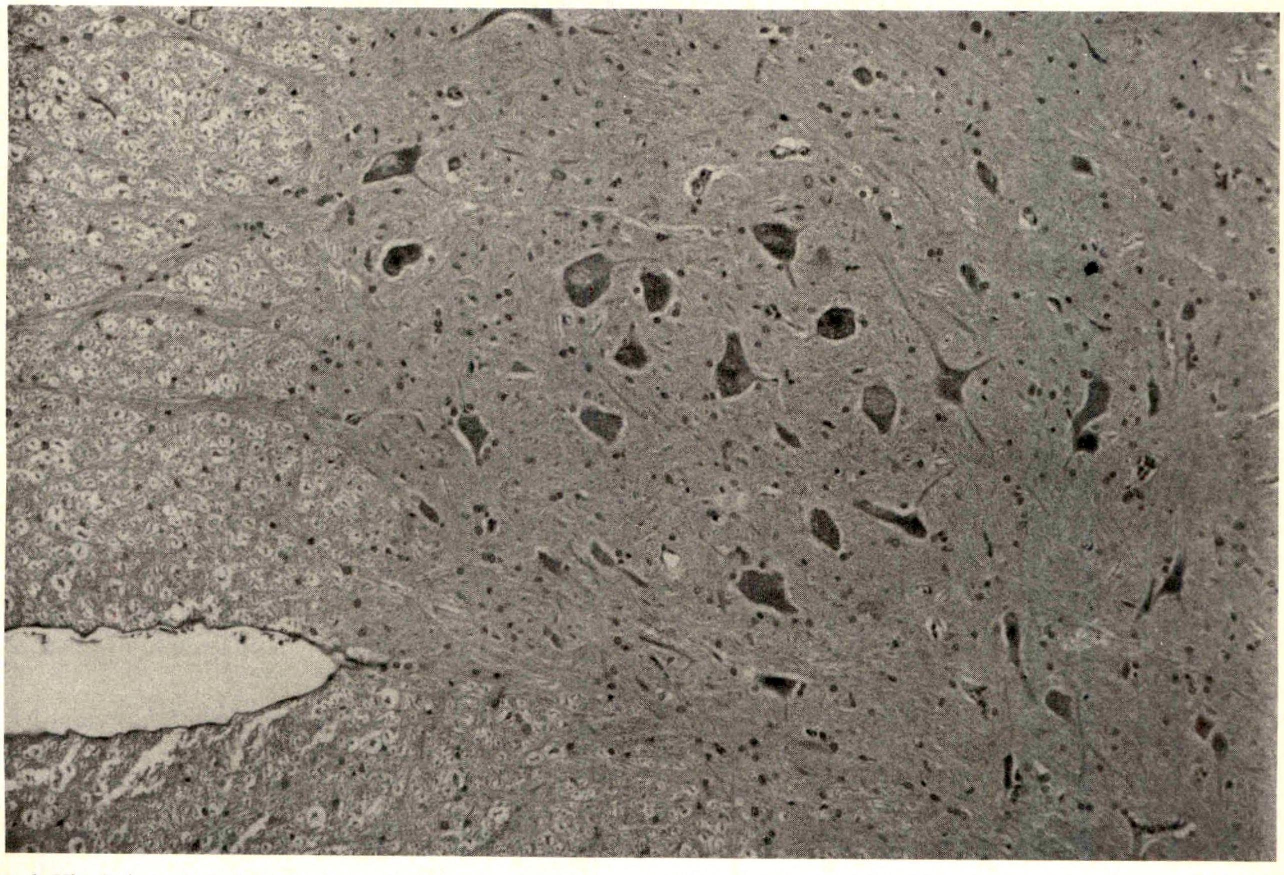

FIG. 3. Histologic section of anterior horn of rabbit spinal cord in an animal that remained neurologically normal. Ganglion cell architecture is normal.

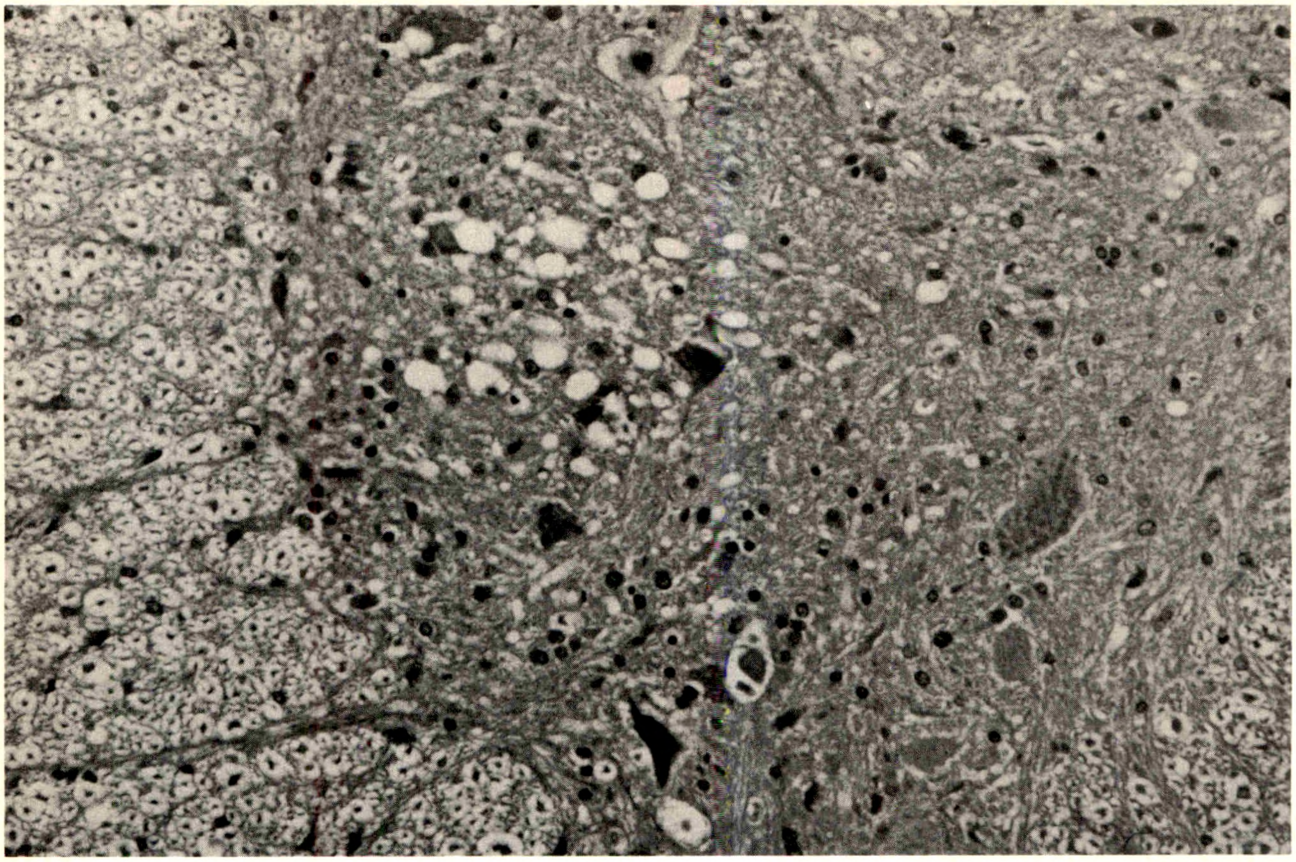

FIG. 4. Histologic section of rabbit spinal cord taken from an animal with delayed-onset paraplegia. Note the presence of both viable and nonviable ganglion cells as well as vacuolization within the anterior horn.

aneurysm and the level of aortic cross-clamping.[2] Reported risk of neurologic deficits after thoracoabdominal aortic reconstruction has been reported between 5% and 30%.[1,2] However, some patients awaken from anesthesia with acute-onset paraplegia and others develop delayed-onset neurologic deficits over the following 1 to 5 days.[16]

A rabbit model of spinal cord ischemia has been developed that produces borderline ischemia, resulting in the development of both acute and delayed-onset paraplegia.[4,14,15] Rabbits have a segmental blood supply to their spinal cord with poor collateral flow between segments. By clamping the infrarenal aorta, the adjacent spinal cord is rendered ischemic yet with minimal hemodynamic effects. Occlusion of the infrarenal rabbit aorta for a period of 21 minutes is associated with both acute paraplegia in some animals and delayed-onset paraplegia in others.[4] Such clamping results in rapid loss of initially motor and then sensory function; restitution of aortic blood flow results in the return of sensory function before motor function.[4] This is a reliable model for producing neurologic deficits from ischemic spinal cord injury, and we believe that it provides an excellent model to explore the pathophysiology of spinal cord ischemic injury, including acute and delayed neurologic deficits. It also allows one to identify potential interventional modalities that might serve to protect the spinal cord from ischemic injury. Using this model, we have evaluated the influence of hypothermia as well as three different anesthetics on ischemic spinal cord injury.

Tissue ischemia occurs when metabolic demand exceeds the nutrient supply of glucose and oxygen. Approximately two thirds of the energy consumed by the central nervous system (CNS) is used to support the electrophysiologic function.[17] Examples include stabilization of ionic gradients and the synthesis and transport of neurotransmitters. The remaining one third is used for cellular homeostasis, in other words, for retaining the stability of neuronal membranes.

Hypothermia has many different effects on the CNS.[18–22] Primarily, the metabolic rate is reduced by 6% to 7% per degree Celsius the core temperature is reduced.[20] In light of obvious reduction in blood flow caused by aortic clamping, it is logical that a reduction in CNS metabolic demand, as occurs in lowering the body temperature to 30°C, might reduce the risk of ischemic neurologic injury. Hypothermia has other effects that also would seem to be protective to the ischemic spinal cord. Hypothermia decreases secretion of cerebrospinal fluid, which results in

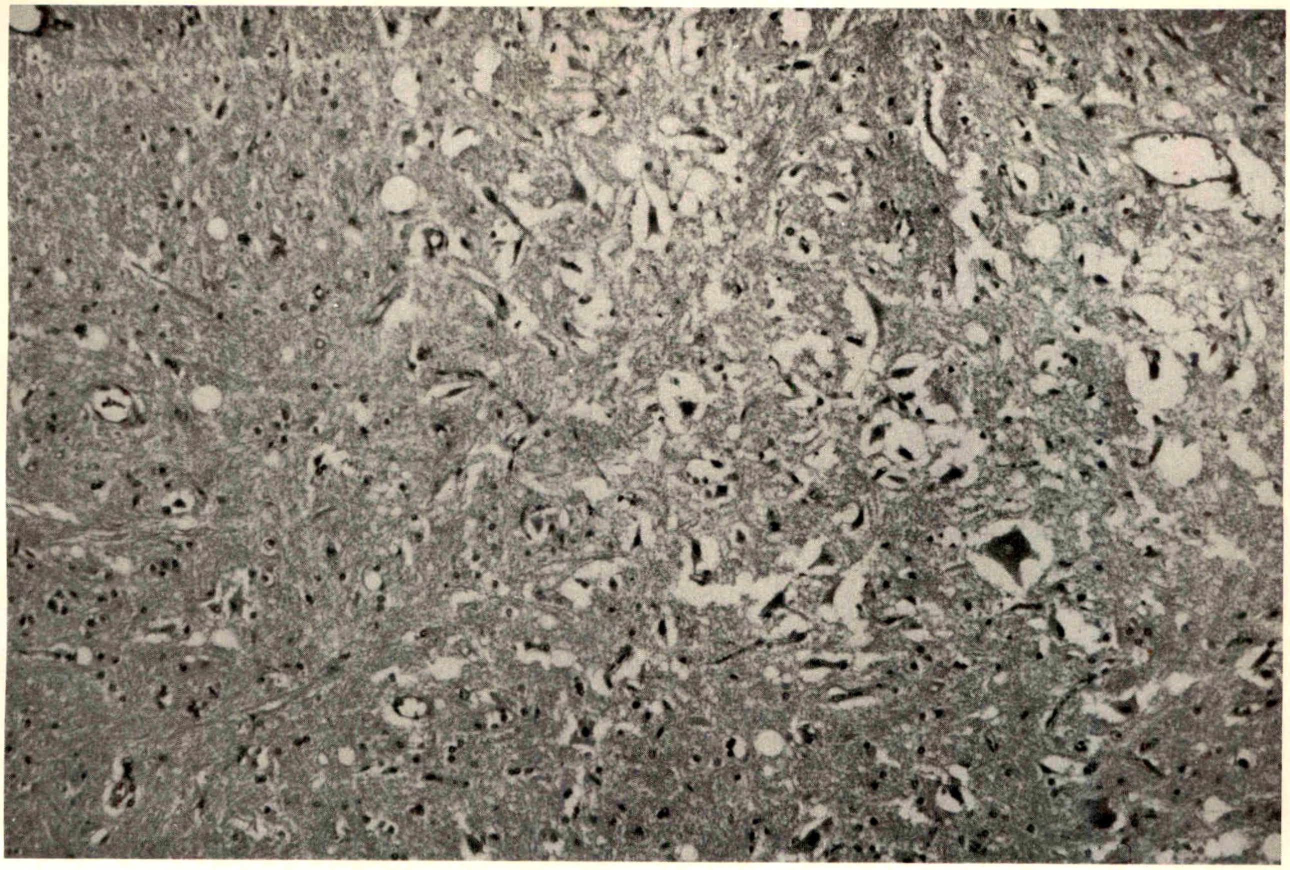

FIG. 5. Histologic section of rabbit spinal cord taken from an animal with acute-onset paraplegia. Note the complete destruction of ganglion cells and extensive vacuolization of the anterior horn.

a reduction of cerebrospinal fluid pressure.[21,22] Reduction in cerebrospinal fluid pressure facilitates spinal cord perfusion by favorably affecting the perfusion pressure.[7]

The protection afforded by hypothermia is not only limited to the acute phase. Limiting the extent of spinal cord ischemia can reduce delayed neurologic deficits.[4] Patients who suffer ischemic injury to the spinal cord do not necessarily have immediate destruction of the spinal neurons. Over time, secondary cell death occurs, which in part may be due to cord edema, activated leukocyte injury, or vasoconstriction stimulated by metabolites of arachidonic acid.[4,8–13] Hypothermia reduces intracranial pressure, which in turn can limit edema formation.[23] In sharp contrast, fever has been shown to increase CNS edema formation.[23] Therefore, by the mechanisms outlined above, hypothermia should be effective in reducing both acute and delayed neuronal injury after aortic cross-clamping. We have demonstrated in this study, using the ischemic rabbit spinal cord model, that, regardless of which anesthetic agent was used, hypothermia demonstrated a significantly protective effect on the spinal cord.

Thiopental treatment alone reduced the risk of acute-onset paraplegia from 61% to 17%. Ketamine also appeared protective to some extent against the acute ischemic insult. Halothane showed no effect on final neurologic outcome. Delayed paraplegia was increased from 30% in controls to 75% with thiopental treatment and 50% with ketamine treatment ($p < 0.05$ for thiopental, $p = 0.10$ for ketamine). We interpret these findings as demonstrating some, yet incomplete, protection of the spinal cord by these anesthetic agents, allowing a reduction in risk of acute-onset paraplegia but insufficient protection to prevent the formation of delayed-onset paraplegia. In fact, risk of delayed-onset paraplegia is increased with thiopental and ketamine treatment, likely because acute onset deficits have been shifted to delayed-onset deficits by limiting the deleterious effect of this interval of ischemia.

The differential effects of certain anesthetic agents on the ischemic spinal cord is basically predictable based on their CNS effects. Thiopental reduces CNS metabolic rate and relaxes CNS vascular smooth muscle, thereby augmenting blood flow.[24–29] Another important mechanism in the protective effect of thiopental is its property of lowering CNS pressures.[30] Decreased CNS pressure increases spinal cord blood flow and limits edema formation. Therefore, for multiple reasons, thiopental will serve a protective effect on the ischemic spinal cord.

The actions of ketamine are manyfold, and no clear-cut effect on the spinal cord can be predicted. Unlike barbiturates, ketamine increases CNS metabolic rate, and it has been shown to increase the cerebral metabolic oxygen demand.[31] It also increases the intracranial (and probable spinal) pressure.[32,33] Yet it may serve a protective effect on the cord by causing vasodilatation of the CNS vascular tree.[34] In our study, ketamine reduced the incidence of neurologic insult, but not significantly ($p < 0.10$).

In sharp distinction to thiopental, halothane is to be avoided in procedures in which spinal cord ischemia is a risk. Halothane impairs the intrinsic autoregulation of blood flow to the CNS.[35] Some authors suggest that halothane causes an uncoupling of the cerebral blood flow and metabolism.[36] Despite early increases in CNS blood flow during halothane inhalation, there then occurs a precipitous drop in CNS perfusion, which may take anywhere from 2 to 5 hours to return to baseline.[37] Therefore, even after reperfusion, CNS tissues may remain relatively ischemic because of this delayed halothane action. Central nervous system water accumulation is greater over the 24-hour period after halothane anesthesia, a feature that contributes to increased CNS pressure and edema formation.[38] In a rabbit study, Forster et al.[39] demonstrated that halothane anesthesia reduced the protective effect of the blood–brain barrier; a study in humans also suggests that halothane can interfere with the functioning of the blood–brain barrier.[40] These facts all taken together would support our findings that halothane does not serve a protective effect on the ischemic spinal cord. It would follow that halothane may even be detrimental to the spinal cord, especially after a time of marginal perfusion.

In summary, we have used a rabbit model of spinal cord ischemia that mimics the situation seen in patients undergoing thoracoabdominal aortic aneurysm repair. Some animals develop acute paraplegia, and others demonstrate delayed onset of neurologic deficits. Thiopental, a barbiturate, is moderately protective to the ischemic cord, whereas ketamine and halothane demonstrate no significant differences as compared with controls. Hypothermia significantly reduces the incidence of neurologic deficits regardless of the anesthetic agent used. We conclude that hypothermia and barbiturate treatment during aortic cross-clamping are protective to the ischemic spinal cord and may be beneficial as adjunctive measures to prevent spinal cord injury secondary to ischemia.

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DISCUSSION

DR. DENTON A. COOLEY (Houston, Texas): Forty years ago almost to the day in 1951, at the meeting of the Southern Surgical Association at The Homestead, we presented the first paper recommending a direct aggressive surgical repair of aortic aneurysms. Previously, only a few reports of aneurysmal excision had been reported. In that presentation, we discussed the threat of spinal cord injury when the descending thoracic aorta was temporarily occluded to permit aneurysmal repair or excision. Since then, surgical treatment of aneurysms has evolved to repair of the aorta and restoration of circulatory continuity with a prosthetic graft.

One of the major problems that remains, however, is ischemic injury to the spinal cord during aortic cross-clamping of the descending aorta. Avoidance of postoperative paraplegia has challenged, confounded, and often mystified surgeons during this era. The experimental technique in rabbits reported last year and amplified here by Dr. Hollier and his associates should be a useful means of investigation in this challenging area. In our laboratory studies in adult pigs, we have obtained favorable results with regional hypothermia of the spinal cord by using perfusion techniques.

Dr. Hollier's group has also reported the effects of anesthetic agents on the incidence of paraplegia. Recently, we reported the protective effect of nimodipine, a calcium antagonist, on the incidence of paraplegia after aortic cross-clamping. Many factors may be responsible for neural injury, but most data suggest that elevated levels of intracellular calcium play a major role. This discussion has been given without access to Dr. Hollier's paper, so I would like to ask Dr. Hollier whether he has considered the effect of anesthetic agents on spinal fluid pressure. Inhalation anesthetics such as halothane increase cerebral spinal fluid pressure, whereas barbiturates have no such effect.

Recently, we have repaired aneurysms in our patients by using an "open" type repair in which we apply only a single proximal aortic clamp. An autotransfusion device is used to capture the blood from the lower circulation. Under these conditions, spinal fluid pressure and central venous pressure are reduced. The open technique in addition to decreased periods of aortic occlusion may account for the absence of neurologic complications among 27 consecutive patients who underwent repair of their aneurysms at our institution.

I compliment the authors, Drs. Naslund, Hollier, and others, on this interesting contribution. Will they comment further on spinal fluid pressure relationships in their experiments? Thank you.

DR. WILLIAM W. MONAFO (St. Louis, Missouri): I would like to add my congratulations to Dr. Hollier and his associates on a very nice study, and it is a beautiful presentation. I would like to pass along a few observations that we have made in the laboratory using the rat, which may or may not resemble the guinea pig or the human. But in the normal rat, pentobarbital anesthesia (not thiopental as Dr. Hollier has used) results in the reduction of spinal cord blood flow in a normal rat. Conversely, when the rat is made hypothermic to the range that Dr. Hollier has recorded, that is, at around 30 C, spinal cord blood flow actually increases by about 25%. Moreover, the increase associated with hypothermia in the rat seems to be mediated, in part at least, by the sympathetic nervous system. And I would like to pass that information along to Dr. Hollier and ask him if he has in fact examined the effects of these anesthetic agents on regional blood flow in his model. Thank you.

DR. G. MELVILLE WILLIAMS (Baltimore, Maryland): I, too, want to congratulate the authors on presenting a significant study in helping us understand the increasing vexing problem of delayed paraplegia after spinal cord ischemia. They have shown previously that ischemic time is the major determinant of recovery, delayed paralysis, or immediate paralysis, and have not only confirmed this finding in this study, but have provided convincing evidence that agents known to protect the brain from ischemic injury also protect the spinal cord. Thus, I find it strange that an ischemic event should have overt manifestations hours or even days later. We do not have a sizable number of patients developing strokes hours or days after carotid surgery. When we do, we look for a cause and generally find one. That is my first question, whether the authors would accept the hypothesis that delayed paraplegia is a two-hit phenomenon. Ischemia would be the initial hit, causing cord swelling, and a second, perhaps even mild, circulatory insult would provoke this spinal cord stroke. Second, the amelioration of initial ischemia by hypothermia seems to solve the problem, as you have shown, because it also defeats the ischemic event. The profound beneficial effects that you have demonstrated should find clinical application rapidly. Thus, my second question is, how do we introduce hypothermia best into an already complex operation? Thank you.

DR. LARRY H. HOLLIER (Closing discussion): I would like to thank the discussants for their probing questions. Dr. Cooley, you are actually one of the major reasons why I got involved in all this to begin with. I happened to read an article that you had written with Dr. Blaisdale in 1962, demonstrating in the dog model the benefits of cerebral spinal fluid (CSF) drainage in that model. You questioned whether these drugs change spinal fluid pressure. They certainly do, as you demonstrated in the past. We have been using CSF drainage in our previous experimental work and have demonstrated in the dog model and in the rabbit model that CSF drainage does have an influence on perfusion. Miamoto in Japan has demonstrated the same thing. We have used nimodipine in humans. I have stopped that for the moment because I have had some unexplained massive vasodilation that occurred throughout the body, and I have not learned exactly how to handle that yet. So we are back to the laboratory with the nimodipine to look at the control of some of the side effects. Dr. Monafo, I appreciate your comments. We have noticed the effects on regional blood flow, but the major effect is of the ischemia itself. Once you develop significant ischemia, the reperfusion that occurs is a 20-fold increase in perfusion of the ischemic cord over the baseline. We have not been able to demonstrate any significant differences in regional blood flow and separate that out from the CSF pressures. And, finally, to answer Dr. Williams' comments, I do believe very much that the brain and the spinal cord should behave similarly because they represent the same neurologic tissue. A neuron is a neuron. The differences, I think, are in two aspects. One, because of the relatively poor blood flow to the spinal cord compared with the relatively rich blood flow to the brain, minor differences in reperfusion changes or in changes of pressure can be detrimentally restrictive to the blood flow in the spinal canal and not have that same effect in the brain. But we do demonstrate that edema occurs in both. Could the delayed onset be a two-hit phenomenon? I think it is a two-hit phenomenon, although different perhaps from what you envision. I think we have shown fairly conclusively that the first hit is ischemia. What is the second hit? There is an excellent paper published just in July of this year in *Stroke* by Clark and his colleagues, using the same rabbit model. And in their paper, they used monoclonal antibodies to CD18 adhesion molecules. Basically, what this means is that when you make the tissue ischemic, leukocytes are activated, and they produce a glycoprotein on the surface that fosters their adherence to the endothelial cells and to the neurons. The second hit then is neuronal lysis caused by the oxygen-derived free radicals produced by the leukocytes. I think that is the second-hit phenomenon. Thank you very much.

Intracavitary Repair of Ventricular Aneurysm and Regional Dyskinesia

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Myocardial damage after infarction is a common sequela in patients with coronary occlusive disease. The extent of injury varies and may be localized or diffuse. Since March 1989, the authors have used a new surgical repair technique that employs an intracavitary patch of Dacron fabric or glutaraldehyde-treated pericardium to exclude the hypokinetic or fibrotic myocardial segment. An elliptical configuration preserves the contour and volume of the ventricular cavity. After securing the patch, the ventriculotomy is closed with a simple continuous suture. Through July 31, 1991, 136 patients underwent repair using this technique. Of these patients, 100 (group I) had neither sustained an acute myocardial infarction (within 30 days before surgery) nor had undergone previous cardiac surgery, whereas 36 (group II) had sustained an acute myocardial infarction or had undergone previous cardiac surgery. In group I, four (4%) died within 30 days of surgery, and seven died later, resulting in a 6-month survival of 90.5% and a 1-year survival of 85.3%. In group II, 11 (30.6%) died within 30 days of surgery, and three died later. Functional class improved after repair in 95.7% of patients in group I and all patients in group II. In both groups, ejection fraction improved significantly ($p < 0.0001$, group I; $p < 0.0001$, group II). By eliminating the need for epicardial buttresses to repair the ventriculotomy, myocardial revascularization has been possible in most patients. This method of intraventricular repair is also appropriate for patients with calcified aneurysms, acquired ventricular septal defects, and acute ventricular rupture.

LEFT VENTRICULAR ANEURYSM and dyskinesia are common complications of myocardial infarction (MI). Minor insults may result in only local dyskinetic areas, whereas more extensive injury, as in transmural infarction, may produce a large aneurysm or even cardiac rupture. In 1958, Bailey and associates[1] reported treatment of ventricular aneurysms by tangential excision of the sac and ventriculorrhaphy in six patients, with five survivors. These cases, begun by Likoff and Bailey in 1954,[2] were the earliest instances of surgical treatment of ventricular aneurysm before cardiopulmonary bypass became available. Because the heart was still beating, however, there was a greater risk that intracavitary thrombi would dislodge and trigger a massive embolism.

In 1958, we[3] performed the first definitive repair of left ventricular aneurysm by using cardiopulmonary bypass. The year before, we[4] had first used cardiopulmonary bypass to repair a postinfarction ventricular septal defect. At the American Surgical Association in 1959, we[5] reported six cases of successful excision of left ventricular aneurysms using the pump oxygenator for temporary cardiopulmonary bypass. Two years later, we[6] reported 14 cases of repair of a left ventricular aneurysm using the technique of excision with ventriculorrhaphy. Soon, we began to use felt strips for buttresses on the linear repair. After numerous modifications, this technique became the standard repair for almost 30 years. During that time, we repaired 4298 left ventricular aneurysms.

In each of the modifications, however, the geometry of the repaired ventricular cavity was deformed to varying degrees. In addition, the awkward felt strips complicated the coronary bypass procedure. As a result, ventricular function was often impaired; improvements, if seen at all, were often modest. Many of these patients required early postoperative support with intra-aortic balloon counterpulsation. Since March 1989, however, we have used a new technique to repair ventricular aneurysms with more favorable results. The new technique is designed to maintain left ventricular contour and volume.

Patients

Between March 1989 and July 31, 1991, 136 patients underwent intracavitary repair of left ventricular an-

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eurysm. Of these patients, 100 (group I) had neither sustained an acute MI (within 30 days before surgery) nor had undergone previous cardiac surgery, whereas 36 patients (group II) had sustained an acute MI or had undergone previous cardiac surgery. We have only recently extended the technique of intracavitary repair to include more of these sicker, higher-risk patients.

The preoperative clinical evaluation of each patient included left ventricular ejection fraction and New York Heart Association functional class status. Left ventricular ejection fraction was calculated according to previously described methods.[7,8] Whenever possible, values obtained by contrast ventricular angiography were confirmed by nuclear ventriculography. Postoperative evaluation included left ventricular ejection fraction before hospital discharge and New York Heart Association functional class status at most recent follow-up. Postoperative ejection fraction was determined by using nuclear ventriculography. Improved ejection fraction was defined as a 5% or greater increase in ejection fraction after surgery. Decreased ejection fraction was defined as a 5% or greater decline in ejection fraction after surgery. No change was defined as less than 5% change. In addition, we evaluated early (30 days or less) and total mortality rates.

Group I

The mean age of the patients who had not sustained an acute infarction nor had previous cardiac surgery was 57.9 ± 9.0 years (range, 37 to 78 years). There were 87 men (87%) and 13 women (13%).

The most common locations of the left ventricular aneurysm were anterior-apical (31%), anterior-septal (24%), and apical-septal (26%). Thrombus was found in 45% of the aneurysms. Coronary artery bypass was performed concomitantly in 92 patients (92%). Of these 92 patients, 16 (17.4%) had one bypass graft placed, 28 (30.4%) had two grafts, 33 (35.9%) had three grafts, 13 (14.1%) had four grafts, and two (2.2%) had five grafts. Most (62.2%) of the procedures were done with a combination of saphenous vein and internal mammary artery grafts. Of the remaining procedures, the saphenous vein was used alone in 22.2%, and the internal mammary artery was used alone in 15.6%.

Concomitant procedures other than coronary artery bypass were performed in 14 (14%) of the 100 patients in this group. Other concomitant procedures included implantation of an automatic implantable defibrillator in six patients, endarterectomy of the left anterior descending coronary artery in two patients, endarterectomy of the right coronary artery in one patient, mitral valvuloplasty in two patients, repair of a postinfarction ventricular septal defect in two patients, and electrophysiologic mapping in one patient.

Intra-aortic balloon counterpulsation was used in 22 of the 100 patients (22%). The mean duration of follow-up was 10 months.

Group II

Of these 36 patients, 21 had undergone previous cardiac surgery, and 18 had sustained an MI within 30 days before surgery. These patients were significantly older than patients in group I (64.1 ± 8.3 years; range, 48 to 79 years; $p < 0.0005$), and there were slightly more women (16.7%, six patients) in this group. Locations of the aneurysms were similar; the most common were anterior-septal (33.3%), anterior-apical (25%), apical-septal (16.7%), and anterior-lateral (11.1%). Thrombus was found in 44.4% of aneurysms. Coronary artery bypass was performed concomitantly in significantly fewer patients (29 patients, 80.6%, $p < 0.05$). The percentage of grafts placed, however, was similar: 4 patients (17.6%) had 1 graft, 7 (29.6%) had 2 grafts, 11 (36.3%) had 3 grafts, and 7 (14.3%) had 4 grafts. Most (58.6%) of the procedures were also done with a combination of saphenous vein and internal mammary artery grafts. The percentage of patients who had saphenous vein graft alone in this group was higher (34.5%), and the percentage of patients who had internal mammary artery graft alone was lower (6.9%).

Concomitant procedures other than coronary artery bypass were performed in seven (19.4%) of the 36 patients. Other concomitant procedures included endarterectomy of the left anterior descending artery in one patient, mitral valvuloplasty in three patients, repair of the carotid artery in one patient, repair of a ventricular septal defect in one patient, and electrophysiologic mapping in one patient.

Intra-aortic balloon counterpulsation was used significantly more often in group II (18 patients, 50%, $p < 0.001$). Use of the balloon has decreased in frequency each year, however, from 64% (7/11 patients) in 1989 to 25% (1/4 patients) in 1991, which is the same frequency as that in group I in 1991. The mean duration of follow-up in group II was 5.5 months.

Statistical Analysis

Univariate analyses were performed by using Student's t test, chi square analysis, or Fisher's exact test. The difference between preoperative and postoperative ejection fraction was analyzed by using the paired t test. A p value of 0.05 or less was considered statistically significant.

Surgical Technique

The usual median sternotomy is made.[9] Single, large-bore cannulae are used to cannulate the ascending aorta (arterial) and right atrium (venous). Bicaval cannulation is used when mitral repair is indicated. The operation is performed during cardiopulmonary bypass with moderate hypothermia (26 to 28 C). Cold crystalloid cardioplegic solution containing potassium chloride is delivered antegrade through a large-bore needle in the ascending aorta to produce asystole and myocardial relaxation. The needle then is secured in the ascending aorta and used to vent the left side of the heart during the repair. To repair anteroseptal aneurysms, an incision is made into the ventricle, 2 cm lateral and parallel to the left anterior descending coronary artery. To repair posterior aneurysms, an incision is made through the aneurysm posteriorly.

After blood has been evacuated from the heart, we identify the transition zone between scarred and normal myocardium. The whitish, fibrous scarring contrasts easily with the more normal, maroon-colored myocardium. Next, we estimate the extent of the defect in the ventricular wall, to prepare an appropriately sized prosthesis. The prosthetic patch must be tailored according to the size and shape of the ventricular cavity, and its length and width should conform to normal left ventricular volume (usually 2 × 4 cm). We generally use woven Dacron for the patch, although on occasion we have used glutaraldehyde-treated bovine pericardium. Although both materials can be used successfully, we prefer the Dacron patch.

The patch, which should extend under, but not into, the ventriculotomy, is secured with a 3–0 polypropylene continuous suture. At this stage, caution should be used to avoid damaging the papillary muscles. Next, we repair the ventriculotomy with a continuous double row of sutures (Fig. 1). We have found that the felt strips are no longer necessary for buttressing, because the ventriculotomy is not exposed to intracavitary pressure. Moreover, felt strips may be subject to infection and late pseudoaneurysm formation. Care must be taken not to cross the interventricular groove or the left anterior descending coronary artery with sutures, even when the artery is severely diseased or totally occluded.

In some patients, where feasible, myocardial revascularization should be performed simultaneously with aneurysmal repair. The left internal mammary artery is used to bypass the left anterior descending artery when a lumen is present, even though the left anterior descending may be small and fibrosed. The other coronary arteries are bypassed with a reversed saphenous vein graft, which should be carefully prepared to avoid injury. Finally, heparin is reversed with Coumadin (warfarin).

Results

Group I

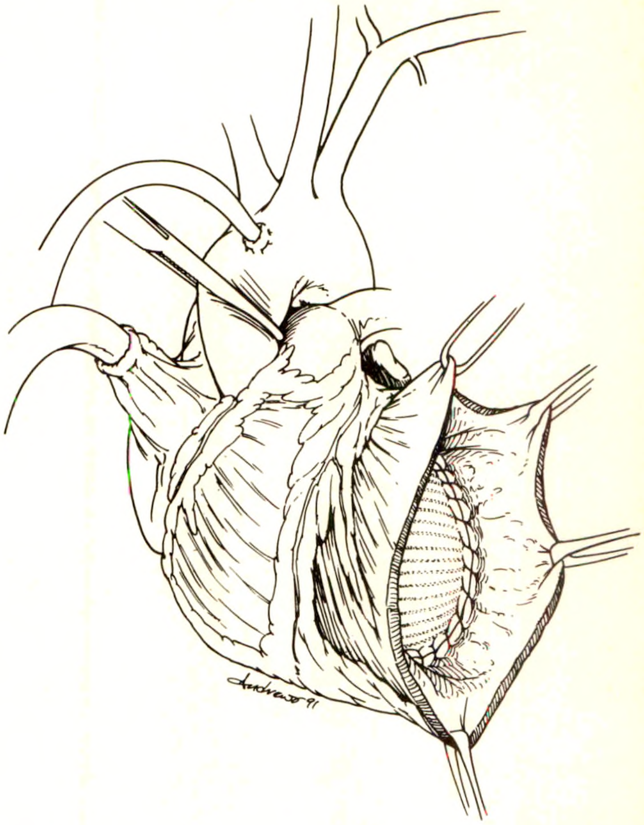

FIG. 1. Technique of intracavitary repair of a left ventricular aneurysm using a patch of woven Dacron fabric.

Before intracavitary repair, 96 (96%) of the 100 patients who had neither sustained an acute infarction nor undergone previous cardiac surgery were in New York Heart Association functional classes III and IV. In contrast, after intracavitary repair, only three (4.3%) of 69 patients with follow-up information available remained in classes III and IV. Of the 69 patients studied, functional class improved after repair in 66 (95.7%). Functional class did not worsen in any patients.

Ejection fraction also improved significantly after intracavitary repair. When we compared the differences between preoperative and postoperative ejection fractions (both measured before discharge) in 70 patients for whom data were available, we found that ejection fraction increased in 75.7% (53 patients), remained the same in 20% (14 patients), and decreased in only 4.3% (three patients). The mean change in ejection fraction was 10.9 ± 1.2 ($p < 0.0001$).

There were four deaths (4%) within 30 days of surgery. Three of the patients died of ventricular tachycardia, and the other patient died of sepsis. The mean preoperative ejection fraction of these patients was 26.7 ± 2.9. Their mean age was 52.8 ± 15 years.

There were seven late deaths. Two of these patients died of myocardial failure, one died of arrhythmia, one died of sepsis, one died of multiple system failure, and two died of undetermined causes.

At 6 months, survival was 90.5%, and at 1 year, survival was 85.3%.

Group II

Before intracavitary repair, all of the 36 patients who had sustained an acute infarction or who had previous cardiac surgery were in New York Heart Association functional classes III and IV. At follow-up, data on functional class (available for 15 patients) showed improvement in all patients.

Ejection fraction also improved significantly in this group of extremely high-risk patients. When the differences between preoperative and postoperative ejection fractions (both measured before discharge) were compared for 20 patients for whom data were available, we found that ejection fractions increased in 85% (17 patients), remained the same in 15% (3 patients), and did not decrease in any patients. The mean change in ejection fraction was slightly better in this group (13.4 ± 2.3), but it was not statistically significant.

In this high-risk group, there were significantly more deaths (11 patients, 30.6%, $p < 0.0001$) within 30 days of surgery. Five of the patients died of low output syndrome, two died of ventricular tachycardia, one died of cardiogenic shock, one died of left ventricular dysfunction, and two died of unknown causes. The mean preoperative ejection fraction of these patients was 27.8%. Their mean age was 66 ± 8 years.

There were three late deaths in this group. One patient died of multiple system failure, one died of low output syndrome, and one died of undetermined causes.

Discussion

Intracavitary repair of ventricular aneurysms restores the shape and volume of the left ventricle. The fabric patch compartmentalizes the left ventricle, creating an anatomically correct intracavitary space. We believe that this space, which is incorporated into the wall of the left ventricle, may account for the good functional results achieved in these patients. Because the surface of the ventricle is not distorted, ventricular function may return to normal while paradoxical contractile forces are controlled (Fig. 2). This improvement occurs because the patch, even though noncontractile, stabilizes ventricular contraction during systole. Stress is taken off the ventriculotomy, which controls hemorrhage.

The technique of intracavitary repair resembles the technique of arterial aneurysm repair proposed by Rudolph Matas[10] more than a century ago, and Matas called his technique endoaneurysmorrhaphy. The technique also conceptually resembles the repairs proposed for ventricular aneurysms by Jatene[11] and Dor and colleagues.[12] Both techniques attempt to restore normal left ventricular volume, contour, and anatomy. Jatene, however, operates on a beating heart. Additionally, the Jatene repair uses an internal purse-string suture placed at the transition

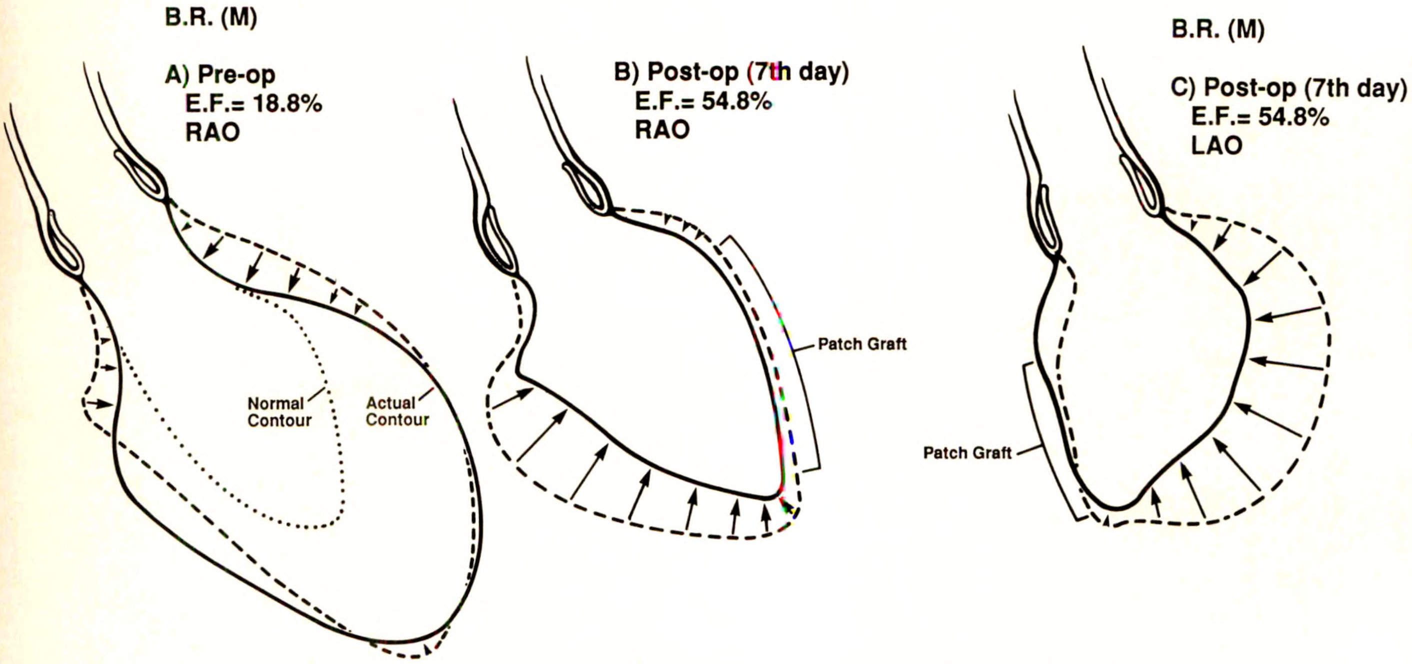

FIG. 2. Computer-enhanced ventriculograms showing a typical increase in ejection fraction in a patient after intracavitary repair. Reprinted with permission from Cooley DA. Ventricular endoaneurysmorrhaphy: a simplified repair for extensive postinfarction aneurysm. J Cardiac Surg 1989; 4:200–205.

from normal to fibrous tissue. These sutures, which are pulled before rebuilding the cavity, may later become detached if placed under stress.

Like the Jatene technique, the technique proposed by Dor also involves suturing the epicardial surface. Dor's technique of ventriculorrhaphy emphasizes aneurysmal excision and replacement with a pericardial-covered Dacron patch. Hemorrhage that may occur when the suture line is placed under stress with this technique could be avoided by intracavitary repair.

Intracavitary repair is simpler than either the Jatene or Dor technique and, in addition, does not distort the outer surface of the ventricle. Intracavitary repair may be extended to patients with a number of related diagnoses. We perform intracavitary repair in patients with localized areas of myocardial fibrosis and decreased ventricular function. We have used the technique in patients with more diffuse dyskinesia, because the repair enhances the function of less dyskinetic areas of the ventricle. In addition, the technique may be used to repair calcified aneurysms[13] and aneurysms on the posterior ventricular surface. We also have extended the technique to cover postinfarction ventricular septal defects[14] and, most recently, to more patients with acute MI. Even though the risk in these patients is higher, in our series postoperative ventricular function and functional class improved significantly, even more than in patients in group I.

Intracavitary repair may benefit patients with ventricular tachycardia, because the exciting focus is usually at the junction of the scarred and normal tissue. Electrophysiologic testing either before or during the operation can determine the exact location of arrhythmogenic foci. In patients with arrhythmias, locating the arrhythmogenic focus is critical. In our series, death can be attributed mostly to arrhythmias in 36.4% of the patients in group I who died and 14% of the patients in group II who died. Thus, when the exciting focus is in an area that may continue to produce life-threatening arrhythmias after repair, cryoablation or subendocardial resection should be considered. In some patients with multiple foci, an automatic implantable defibrillator may be needed.

We have found that felt buttresses, which are customary in conventional repair of ventricular aneurysms, are unnecessary with this technique, because the Dacron patch

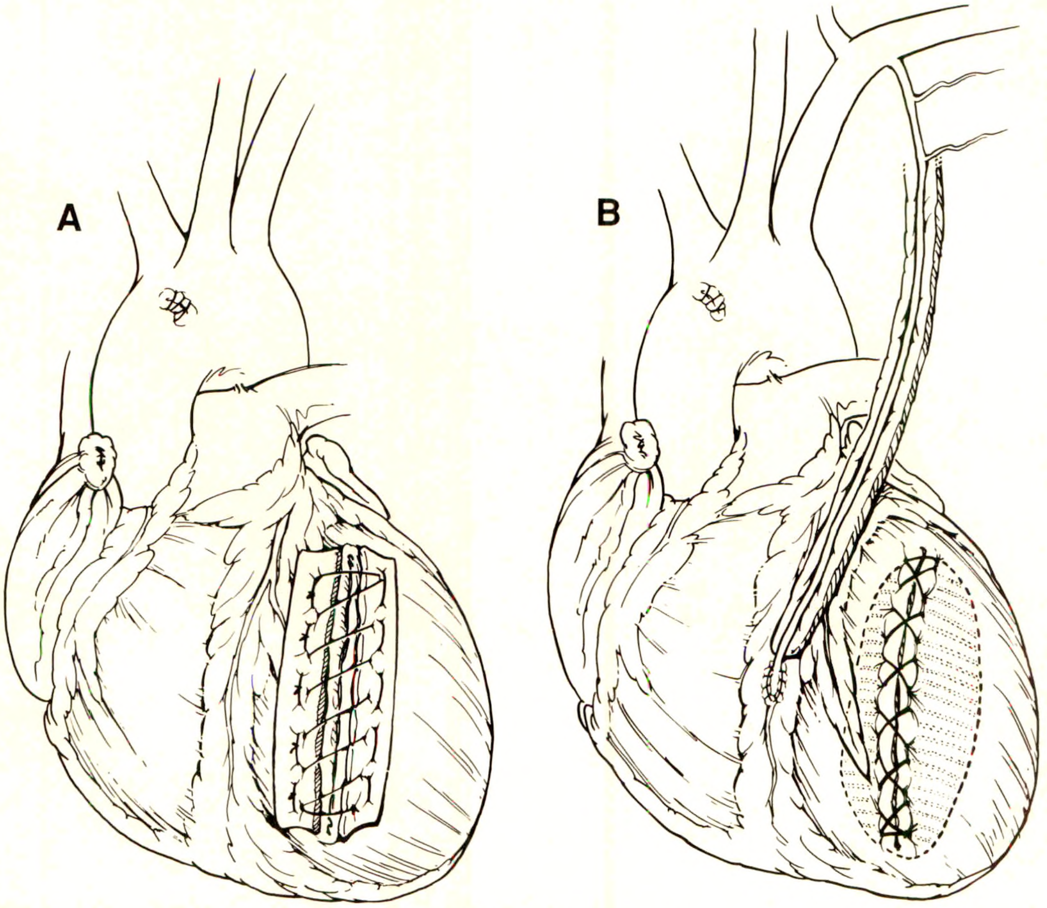

FIG. 3. Comparison of (A) conventional repair and (B) intracavitary repair of left ventricular aneurysms. Intracavitary repair does not require felt buttresses and permits accessibility of the anterior descending artery for revascularization.

stabilizes the ventricle (Fig. 3). In our opinion, other types of buttresses such as autologous pericardium are also unnecessary.[15] Eliminating the felt strips preserves the surface anatomy of the heart and avoids the possibility of subsequent infection from the foreign material. When infection occurs, recurrent ventricular pseudoaneurysm may follow.[16] In one recently published case from another institution, the pseudoaneurysm was secondary to infection of the cardiac suture line, caused by a pathogen residing in the multifilamented Teflon strips.[17] In a similar case from our institution, a patient recently underwent his fourth aneurysm repair. In this case, a pseudoaneurysm had formed at the site of infection in the Teflon strips. We repaired the aneurysm by using a double internal patch of pericardium below with woven Dacron above (Figs. 4 and 5).

In addition, we have performed intracavitary repair on four patients who were initially admitted for evaluation of cardiac transplantation. These patients had severe ventricular dysfunction characterized by large ventricular aneurysms, with an average preoperative ejection fraction of 14% (range, 10% to 20%). Each of the patients was successfully treated by this technique, thus avoiding the need for transplantation. Postoperative ejection fraction in these patients averaged 34.3%. Two of these patients are well and have resumed normal activities. Two patients died suddenly, one at 3 months and the other at 7 months after operation.

The difficulty that remains for us is to define what constitutes a left ventricular aneurysm as opposed to dyskinesia. Definitions vary, but most pathologists and surgeons agree that a ventricular aneurysm is a thin, stretched area of the ventricle, characterized by scarring and fibrous tissue. Many cardiologists, however, view the aneurysm as that part of the ventricle that expands during systole, regardless of the type of tissue. Even among surgeons, there is disagreement regarding where an aneurysm stops and dyskinesia begins. In addition, aneurysmal size is seldom considered in analyses.[18-20] As a result, it is difficult to compare postoperative function with patients who have undergone conventional repair.[21]

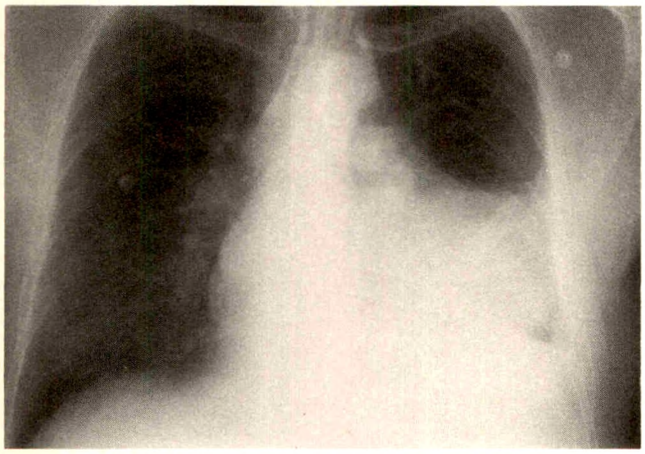

FIG. 4. Chest roentgenogram of a patient with a recurrent pseudoaneurysm caused by an infection that formed at the site of the Teflon felt strips. The patient had undergone three previous procedures. His aneurysm was successfully repaired by the intracavitary technique.

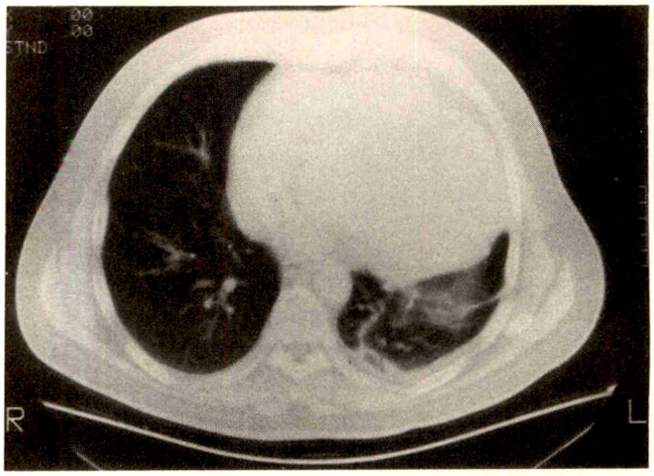

FIG. 5. Computed tomography scan of the patient with recurrent pseudoaneurysm (see text and Fig. 4).

In summary, by preserving both the internal contour and the surface anatomy of the ventricle, intracavitary repair allows better physiologic function to be achieved in patients undergoing repair of left ventricular aneurysms. In addition, myocardial revascularization can be performed more easily, because buttresses are not used. We believe the technique can be used on all ventricular aneurysms, but is especially suited for large, diffuse aneurysms that are not amenable to plication or resection. Our results show that even the largest ventricular aneurysms are amenable to surgical repair, as long as active myocardium is demonstrated on ventriculography.

Acknowledgments

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DISCUSSION

DR. JOHN L. OCHSNER (New Orleans, Louisiana): I would like to open the discussion on this paper. It always amazes me how this Texas group can come up with these new techniques with such limited experience. But they happen to do that from time to time. As Dr. Cooley said, this technique is similar to two others that have been described, both by Jatene and Dor, and yet has some advantages over those two techniques. As he said, it still stabilizes the ventricular contraction, and I do not think it seems to have any constraints on the diastolic enlargement. Dr. Dor's technique is very similar, but he cuts off the ventricular muscle because he thinks that allows better diastolic filling to occur, whereas closing it would constrain the diastolic size. But I think Dr. Cooley has shown very well that this does not occur, because there is enough tissue left over that it is very loosely held and the diastolic enlargement continues. This technique also has the advantages of lessening stress on the suture line and decreasing hemorrhage, which is a problem in some of the other repairs. I was a little concerned or confused as to why, in the 100 cases that were in the elective group, there was a 22% use of the intra-aortic balloon pump, whereas in your paper you said in the last year you only used the intra-aortic balloon in 25% of even the very-high-risk group. Were the balloons used just as a prophylactic measure, or were these people really in need of it? There obviously is a difference in the two groups. But I would like to again compliment Dr. Cooley and his group because I think this is really an improvement in the technique of repair of ventricular aneurysms and will help all the cardiac surgeons in their treatment.

DR. ROBERT A. GUYTON (Atlanta, Georgia): Thank you, Dr. Ochsner. I appreciate the opportunity to discuss this paper and also the opportunity to review the paper before the meeting this morning. Dr. Cooley brings to us 33 years of experience with repair of ventricular aneurysm and more than 4500 aneurysm operations, which is outstanding, obviously the largest experience in the world. I'm still searching — and I think we all are still searching — for the proper role of ventricular aneurysm repair. The decision in the case of the patient such as the one Dr. Cooley showed with the large grossly dyskinetic aneurysm is easy. But a more familiar and more difficult problem is a patient with three-vessel coronary disease, a moderate-sized akinetic or slightly dyskinetic apical aneurysm, and mixed symptoms of disabling angina and moderate congestive heart failure. It is easy to respond that the presence of a 4-cm, easily resectable apical aneurysm is sufficient reason for repair, particularly if one has developed an elegant operation such as the one presented here. But I have found out — and I know everyone else has — that ventricular aneurysm repair is not without problems. I vividly remember one patient in whom ventricular tachycardia was not a problem before operation, but after operation medically uncontrollable ventricular tachycardia led to that patient's death. In this series, there were four patients whose intrahospital deaths were attributed to ventricular tachycardia.

The second problem that I have encountered is systemic embolism after aneurysm repair in a patient who had no such problem before operation. Indeed, this patient had no intracavitary clot before operation. This is a fantastic series using an ingenuous new operation, but the overall mortality rate in 136 patients was 11%, and postoperative ventricular tachycardia was a problem. I am very eager to use the operation for large or dyskinetic aneurysms, but I remain uncertain about the moderate-sized ventricular aneurysm.

I would ask the authors three questions. First, was postoperative ventricular tachycardia a recognized or difficult problem, and were prophylactic antiarrhythmic agents used? Secondly, because these Dacron grafts are obviously sealed by clot, was systemic embolism a problem, and was postoperative anticoagulation used? And finally I would ask the authors to discuss the management of a coronary bypass patient who has a 5-cm apical aneurysm with mild congestive heart failure. This aneurysm is easily repairable, and I would seek the authors' help in deciding whether such repair is really in the best interest of my patients. I think this is a marvelous series, and I would like to thank the Association for the privilege of discussing the paper. Thank you.

DR. MARTIN H. MCMULLAN (Jackson, Mississippi): Dr. Cooley and his group once again have demonstrated their technical wizardry. We as cardiac surgeons all benefit, as do our patients. I am particularly interested, however, in one subset of patients, and those are the patients with acute blowout rupture after myocardial infarction. We have had 11 of these patients since 1980. Four are long-term survivors. Obviously, this is an extremely critical situation, an emergency of the first order. Four of our patients died of brain death because of inadequate perfusion during the resuscitation phase as they proceeded to the operating room. One patient in particular provides us with some insight into Dr. Cooley's technique. This patient underwent successful repair after rupture only to rerupture 12 hours later. The wound was reopened in the intensive care unit. We had used the linear incision technique, and we found that the sutures had pulled through the myocardium where there had been extension of the infarction. All efforts at repair at this point were unsuccessful.

I think had we used Dr. Cooley's technique in this particular situation, this patient might well have survived. This prompts several questions, however. First of all, why are there no large series presented of ruptured hearts? We are told that 4% to 21% of all cardiac care unit deaths and autopsy series are due to rupture. We obviously have failed to raise the index of suspicion of our cardiologists sufficiently to call on us to intervene in this most critical situation. Secondly, is it possible that percutaneous cannulation and emergency cardiopulmonary support may allow us to intervene and prevent that greatest and gravest of all complications, brain death? Thirdly, how does one handle the posterior rupture, or for that matter, the posterior ventricular aneurysm, in the region of the papillary muscles, where the intracavitary repair may be technically much more difficult? And, finally, are there any contraindications to this intracavitary technique? I've enjoyed the paper immensely, and I think it is a tremendous contribution in this area. Thank you.

DR. O. HOWARD FRAZIER (Closing discussion): Thank you, Dr. Ochsner. We appreciate your kind remarks on Dr. Cooley's presentation. To Dr. Ochsner, I would say that the intra-aortic balloon pump is used liberally at our institution, at the discretion of the surgeon, and is generally believed to be helpful. We have found it particularly useful in patients who undergo left ventricular aneurysmectomy.

Dr. Guyton's questions are very pertinent. We believe that the endoaneurysmorrhaphy technique actually minimizes ventricular arrhythmias, and so far, compared with prior techniques, we have found arrhythmias to be less of a problem. We have not seen embolization from the Dacron patch, even though we do not use postoperative anticoagulation. We think that this technique is also of some benefit in a case of postoperative rupture, because it reduces some of the tension on the friable ventriculotomy, so we advocate the use of endoaneurysmorrhaphy in this group of patients.

Particularly, this technique might have been of some benefit in the case of the patient Dr. McMullan presented. Ventricular rupture is a common, fatal complication of acute myocardial infarction. We are not sure why we do not see as many instances of rupture as some other institutions. Part of the reason may be that our institution is not an acute emergency hospital. Of course, the posterior ventricular repair is a problem, but I think this technique, which preserves intraventricular volume, allows for an easier repair of that less common form of ventricular aneurysm.

Assessing and treating the failed myocardium remains one of the greatest challenges for the cardiac surgeon today. Cardiac transplantation is currently the best therapeutic option for this problem. All physicians in the cardiac transplant field recognize the statistical limitations of this treatment in the patient with heart failure. Heart transplantation cannot be used to treat all patients who are dying of heart failure. On the average, only 6 donor hearts are available each day in the United States for the more than 2000 patients awaiting heart transplants. In 1990, the average waiting time for a heart transplant recipient with type O blood was 284 days, and the waiting time for status 2 heart transplant candidates (those who are outpatients) was 422 days. We used to think that people should be accepted for a heart transplant only if they had a high likelihood of dying within 1 year, but the average waiting time for status 2 patients is longer than a year. For status 1 patients (those who are in the intensive care unit), the average waiting time was 49 days, and each day of care in the intensive care unit costs approximately $4000. In addition, there is a problem with long-term survival after heart transplantation.

As a result of all of these problems, we have carefully evaluated each transplant candidate to determine the most effective treatment. In 41 of the 800 patients who have been referred for cardiac transplant evaluation, we have performed conventional rather than transplant surgery. In four of these patients, we used the endoaneurysmorrhaphy technique to repair a ventricular aneurysm. All four patients were discharged, and their average left ventricular ejection fraction improved from 14% to 34%.

I believe that the donor heart shortage and financial limitations of heart transplantation will continue to challenge the cardiac surgeon. Until we have more successful mechanical replacements for the heart, the cardiac surgeon must continue to search for alternative surgical methods for treating the failing native heart.

Thank you very much.

Emergency Coronary Artery Bypass Surgery for Failed Percutaneous Coronary Angioplasty

A 10-Year Experience

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Six hundred ninety-nine patients have required emergency coronary artery bypass after failed elective percutaneous coronary angioplasty during the decade September 1980 through December 1990. This represents 4% of 9860 patients having 12,146 elective percutaneous coronary angioplasty procedures during this interval. Emergency coronary artery bypass was required for acute refractory myocardial ischemia in 82%. Hospital mortality rate for all patients was 3.1%; 3.7% in patients with refractory myocardial ischemia but 0.8% in patients without refractory myocardial ischemia, $p = 0.08$. Postprocedural Q-wave myocardial infarctions were observed in 21% *versus* 2.4%, $p < 0.0001$, and intra-aortic ballon pumping was required in 19% with *versus* 0.8% without refractory myocardial ischemia, $p < 0.0001$. Multivessel disease, $p = 0.004$, age older than 65 years, $p = 0.005$, and refractory myocardial ischemia, $p = 0.08$, interacted to produce the highest risk of in-hospital death. Follow-up shows that there have been 28 additional late deaths, including 23 of cardiac causes for a 91% survival at 5 years. Freedom from both late death and Q-wave myocardial infarction at 5 years was 61%. In the group going to emergency coronary artery bypass with refractory myocardial ischemia, the late cardiac survival was 90%, and in those without ischemia, 92% at 5 years, p = not significant. The MI—free survival in the group with refractory ischemia, however, was 56% *versus* 83% in the group without ischemia, $p < 0.0001$. Multivariate analysis showed the highest late event rates for patients with Q-wave myocardial infarction at the initial emergency coronary artery bypass, age older than 65 years, angina class III or IV, and prior coronary bypass surgery. In spite of a continuing high incidence of early acute myocardial infarction and an increasing operative mortality rate (7%) in the latest 3 years cohort of patients, excellent late survival and low subsequent cardiac event rates demonstrate the lasting effectiveness of prompt, successful emergency coronary bypass surgery for failed percutaneous coronary angioplasty.

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ANDREAS GRUENTZIG VISITED Emory University in 1978, while he was still living in Zurich, when balloon dilatation of the coronary arteries was still in its infancy. During that visit he spent time with our surgical team and said, "For a successful coronary angioplasty program, good cardiology is important; but, superior cardiac surgery is essential." We were pleased that shortly he joined our faculty, where he taught, worked, and practiced until his tragic death in 1985. This report analyzes the first 10 years of emergency surgical support for patients in whom elective percutaneous coronary angioplasty (PTCA) resulted in an acute failure requiring emergency surgical revascularization.

Methods

During the interval September 1980 through December 1990, 9860 patients underwent 12,146 elective PTCA procedures. Six hundred ninety-nine (699) of these experienced failure of balloon dilatation and were thought by the interventional cardiology team to require emergency coronary artery bypass surgery (ECAB). Five hundred twelve (82%) experienced an acute closure syndrome with acute myocardial ischemia that was refractory to all medical, pharmacologic, and angiocatheterization techniques. Chest pain, acute ischemic changes on electrocardiogram, and varying degrees of hemodynamic instability marked this acute ischemia episode. An additional 129 (18%) patients were sent for ECAB who did not experience acute ischemia but in whom the PTCA had failed, and the patient was left with more than 50% stenosis in the target vessel. All these nonischemic patients had an extensive area of myocardium at jeopardy beyond the critical lesions that were believed to be hemodynam-

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ically compromised or at increased risk of acute closure due to the PTCA manipulations.

Thirty per cent of patients having elective PTCA in 1980 were referred for ECAB. In the second year that number dropped to 14%. In the subsequent 9 years, 4% to 6% of PTCA patients have required ECAB.

PTCA Technique

All PTCA procedures were performed using standard techniques, which have been previously described.[1] All patients received aspirin 325 mg and most a calcium channel-blocking agent (nifedipine 10 mg three times daily or diltiazem 30 to 60 mg daily) orally before the PTCA procedure unless a prior history of an adverse or hypersensitivity reaction was present. Before attempted balloon dilatation, diazepam 5 to 10 mg, atropine 0.6 to 1.0 mg, and heparin 10,000 to 15,000 units were given intravenously.

Surgical Backup Protocol

In the first 2 months of this experience, one operating room was kept open and fully staffed with perfusion, cardiac anesthesia, surgical, and nurse teams available any time a PTCA was performed. In subsequent months and years there has been no formal coordination between the PTCA and operating room surgical schedules. When an acute closure episode after PTCA indicated the need for ECAB, that patient was accommodated in the next available operating room (four rooms dedicated per day to cardiac surgery at Emory and two per day at Crawford Long).

The ECAB was performed by the next available surgeon and team. Coordination of this effort was the responsibility of the cardiac anesthesiologist in charge for the day. Details regarding this ECAB protocol, cardiopulmonary bypass techniques, and anesthesia techniques for this risk group have been detailed in earlier articles.[2-4]

Acute Closure at PTCA

The hemodynamic consequences of acute closure of a major coronary artery varied widely from profound cardiogenic shock to only a mild drop in blood pressure. As soon as acute closure was experienced during a PTCA, pharmacologic and angiocatheter measures were instituted in attempts to reopen the closed vessel, reverse the ischemia, and to support the patient's circulation. The ability to maintain even a small amount of blood flow across the injured area was seen to be beneficial. Therefore, splinting the injured zone with the guide wire and more recently an intraluminal stent[5] (Gianturco—Roubin Stent, Cook Inc., Bloomington, IN) or providing an internal translesion flow of blood using a passive autoperfusion catheter reduced the effect of acute ischemia[6] (Stack Perfusion Catheter, Advanced Cardiovascular System, Mountain View, CA). When ischemia persisted despite early measures having been employed, support of the patient using intra-aortic balloon counterpulsation (IABP) was instituted in the angioplasty suite. The value of IABP in this situation was recognized early, and a balloon console was located in the PTCA suite with personnel experienced in its use available.[2]

Coordination of ECAB

When it appeared that a patient required ECAB, the cardiac anesthesiologist in charge of the operating room schedule for the day was notified. This person would then coordinate where the patient could be accommodated and which anesthesia, surgical, nursing, and perfusion teams would be involved. An anesthesia team would be dispatched to the PTCA suite to assist with resuscitation, institute monitoring, provide ventilatory support, and assist with transportation of the patient to the operating suite.[7]

Emergency Surgery Protocol and Cardioplegia

Time of ischemia remains the critical factor. Therefore, rapid induction of anesthesia and institution of cardiopulmonary bypass was sought for all patients, but especially for those with hemodynamic compromise. Extracorporeal circulation was instituted by standard techniques[2] and perfusion was maintained at 2.0 to 2.4 L/minute/m^2. Systemic hypothermia (30 to 20 C), topical hypothermia, and cold potassium crystalloid or blood cardioplegia were used for myocardial protection. Prompt revascularization of the suspected (and often obvious) ischemic zone was performed first. This usually involved placing the first vein bypass graft to the injured vessel to deliver cardioplegia or oxygenated blood past the obstructed zone to the distal ischemic myocardium.[2,3] The normal antegrade delivery of cardioplegia through aortic root injection often did not reach the compromised area because of the complete occlusion of the proximal arterial segment and lack of distal collateral vessels. When a guide wire, autoperfusion catheter, or stent was left across the injured zone, antegrade delivery of cardioplegia was more effective. In these cases, the guide wire or autoperfusion catheter was removed only after the initial administration of cardioplegia was completed. The injured zone was revascularized first with infusion of cold oxygenated crystalloid or blood cardioplegia down each completed graft. More recently, the administration of continuous warm blood cardioplegia retrograde through an indwelling coronary sinus catheter has been employed.[8] After completion of all bypass grafts required, the patient was allowed to rest on cardiopulmonary bypass for an interval with the heart beating but empty. This allowed time for reversal of the effects of the acute ischemia. If IABP had been employed before operation, it was continued for at least until the first postoperative day even if the patient's early hemodynamic recovery indicated that it was not needed.

Selection of Bypass Conduits

Reversed saphenous vein grafts were preferred for most patients and for virtually all patients who arrived in the operating room with ongoing myocardial ischemia. Minimizing the time for revascularization and the ability to infuse oxygenated cardioplegia and blood through a completed vein graft into the distal circulation were obvious advantages for vein grafts and not available if an *in situ* internal mammary artery was used as the conduit for ECAB.

Data Collection

Baseline and restudy demographic, clinical, angiographic, and procedural data, including complications, were recorded prospectively by physicians on standardized forms and entered into a computerized database. Follow-up information was obtained by telephone interviews of the patients or their referring physicians. Follow-up information included occurrence of myocardial infarction since the initial PTCA, subsequent need for an additional revascularization procedure (PTCA or coronary artery bypass graft surgery [CABG]), or death (cardiac or noncardiac). All follow-up information was recorded on standardized forms and entered into the computerized database. In addition, all events noted on forms entered into the database from hospitalization after the initial revascularization was recorded. Follow-up was 98% complete.

Statistical Analyses

Differences in categorical variables were analyzed by chi square, and differences in continuous variables were analyzed by Student's t tests. Overall survival and event-free survival were determined by the Kaplan-Meier method,[9] and probability was expressed as the mean ± standard error of the estimate. Overall survival and event-free survival analyses were performed on the total population, as well as on the subgroups. Endpoints analyzed included (1) survival, (2) freedom from myocardial infarction, (3) freedom from coronary artery bypass surgery, and (4) freedom from repeat PTCA. Comparisons of total and event-free survival were made using the Mantel-Cox method.[10] Correlates of late events were determined by the Cox proportional hazards model.[11] For Cox model analyses, continuous covariates were not broken into groups. All statistical analyses were performed with BMDP statistical software (Los Angeles, CA).

Results

In September 1980, the practice of PTCA began at Emory University. Through December of 1990, 9860 patients had undergone 12,146 elective PTCA procedures. Emergency coronary artery bypass was required in 699 (5.8%), with 574 (82%) having ECAB for ongoing acute myocardial ischemia. Hospital death occurred in 22 (3.1%), with 21 of these in the patients having acute ischemia ($p = 0.097$). New Q-wave myocardial infarction (Q-MI) occurred in 126 (18%) patients and was also concentrated in the ischemia group (123/574 *versus* 3/125, $p < 0.0001$).

Ischemia Status at ECAB

Table 1 presents clinical descriptors for those patients having ECAB divided by the ischemic status at the time of ECAB. No clinical factor could be used to predict the occurrence of acute ischemia at PTCA. Table 2 presents the surgical procedural results analyzed by the patient's ischemic status at the time of ECAB. The need for IABP, the occurrence of a new Q-MI, and an extended in-hospital recovery were highly significant if the patient had ECAB during acute ischemia. Death also occurred more frequently, but at a lower level of significance.

SVD Versus *MVD*

The population's clinical descriptors are analyzed by the presence of single-vessel coronary disease (SVD) *versus* multiple-vessel coronary disease (MVD) in Table 3. Those patients with MVD have a significantly higher incidence of all less favorable clinical characteristics that are known to increase operative risks. Table 4 presents the surgical procedural results analyzed by the presence of SVD or MVD. Those patients with MVD are seen to have a very significantly higher incidence of death, stroke, IABP usage, and required more bypass grafts. The incidence of Q-MI was not different for the two groups.

TABLE 1. *Clinical Descriptors Analyzed by Ischemic Status at Time of Emergency Coronary Bypass Surgery*

Descriptor	Ischemic	Nonischemic	p
N	574	125	
Age > 60 yr	28	31	NS
High blood pressure	42%	48%	NS
Diabetes	15%	14%	NS
CL III–IV	65%	65%	NS
Ejection fraction > 50%	59%	61%	NS
MVD	38%	41%	NS

NS, not significant; CL, Canadian Cardiovascular Society Classification; MVD; multivessel disease.

TABLE 2. *Surgical Results Analyzed by Ischemic Status at Time of Emergency Surgery*

Surgery	Ischemic	Nonischemic	p
N	574	125	
Grafts (mean)	2.0 ± 1	2.1 ± 1	NS
Intra-aortic balloon pump	19%	0.8%	< 0.0001
Q-wave myocardial infarction	21%	2%	< 0.0001
Stay (days [mean])	9.6 ± 10	7.5 ± 2	< 0.0001
Death	3.7%	0.8%	0.09

NS, not significant.

TABLE 4. *Surgical Results Analyzed by Number of Vessels Diseased*

Surgery/Vessel Disease	SVD	MVD	p
N	432	267	
Grafts	1.7 ± .8	2.5 ± 1.1	< 0.0001
Intra-aortic balloon pump	12%	22%	0.001
Q-wave myocardial infarction	18%	19%	NS
Stroke	0.2%	2.3%	0.009
Death	1.4%	6.0%	0.0007

SVD, single vessel disease; MVD, multivessel disease; NS, not significant.

Year of Operation

Table 5 presents the clinical descriptors of this population divided into three separate cohorts by the years of their operations. Clinical factors that increase risk were observed to occur at a significantly increased incidence as the years of this surgical experience progressed. Table 6 presents the surgical procedural results divided into three cohorts by years of operation. The grafts required per patient and the incidence of hospital death have increased, but the need for IABP and occurrence of Q-MI were not different within the 3 cohorts. Of interest is the fact that a significantly higher number of patients presented with acute refractory ischemia in the first two cohorts of patients.

Hospital Death

Univariate and multivariate correlates of in-hospital death are presented in Table 7. Multiple-vessel coronary disease and the more recent years of operation were highly significant in both categories. No other clinical descriptors achieved significance in multivariate analysis. Table 8 presents additional clinical descriptors, all of which were univariate predictors of increased risk of hospital death.

Late Results

Actuarial curves of the 5-year survival and freedom from events are displayed in Figure 1. After the initial hospital mortality rate, the survival rate falls very gradually, with 91 ± 1% alive 5 years after ECAB. Myocardial infarction–free survival is seen to be 61 ± 2% at 5 years, with most Q-MIs occurring during the initial hospitalization. Only 26 patients are known to have experienced the late occurrence of Q-MI. After discharge, the need for subsequent PTCA or repeat CABG was low, 33 and 23 patients, respectively.

TABLE 3. *Clinical Descriptors Analyzed by Vessel Disease Status*

Descriptors/Vessel Disease	SVD	MVD	p
N	432	267	
Age > 60 yr	26%	32%	0.05
Male	71%	82%	0.0007
Prior myocardial infarction	30%	45%	< 0.0001
Diabetes	12%	18%	0.016
Ejection fraction < 50%	8%	25%	< 0.0001
Multisite PTCA	15%	29%	< 0.0001

SVD, Single vessel disease; MVD, multivessel disease; PTCA, percutaneous transluminal coronary angioplasty.

Five-year survival curves analyzed by age at time of ECAB show a significant advantage for those younger than 60 years of age ($p < 0.0001$, Fig. 2). Five-year survival was 94% under the age of 60 years and 81% over the age of 60 years.

Myocardial-infarction–free 5-year survival is analyzed in Figure 3 and shows a wide disparity between those who came to ECAB ischemic *versus* those who are not ischemic, $p < 0.0001$. Myocardial infarction-free survival at 5 years was 56% in the group with acute ischemia *versus* 83% in the group without acute ischemia.

Univariate and multivariate correlates of late survival are presented in Table 9. Age older than 60 years at the time of ECAB and the presence of MVD were found to be significant correlative detrimental factors for 5-year survival by both analyses. Other descriptors achieving only univariate significance in reducing survival at 5 years after ECAB were presence of diabetes, congestive heart failure, reduced ejection fraction, and more recent year of ECAB.

Discussion

The data presented in this paper demonstrate that prompt ECAB has been successful in rescuing patients who experience acute closure after PTCA. Eighty-two per cent (82%) presented to ECAB with refractory myocardial ischemia in spite of full pharmacologic and angiocatheter techniques to reverse the acute ischemia. The operative mortality rate unfortunately has shown a significant increase in the most recent 3-year cohort of patients, (0.5% *versus* 2.4% *versus* 7.1%, $p = 0.0008$). This is observed to have resulted from the more recently operated patients being older with a higher incidence of multivessel disease and clinical descriptors that increase operative risks: di-

TABLE 5. *Clinical Descriptors Analyzed by Year of Emergency Bypass Surgery*

Descriptor/Year	1980–1983	1984–1987	1988–1990	p
No./total PTCA	187/2763	330/4943	182/4440	
Age (yr [mean])	56 ± 9	57 ± 10	60 ± 10	< 0.0001
Age > 60 yr	21%	28%	37%	0.003
Ejection fraction < 50%	8%	16%	20%	0.019
Hypertension	35%	44%	50%	0.008
Diabetes	10%	13%	21%	0.01
MVD	28%	38%	48%	< 0.0004
CL III–IV angina	54%	68%	68%	0.002

MVD, multivessel disease; CL, Canadian Cardiovascular Society Classification; PTCA, percutaneous transluminal coronary angioplasty.

abetes, hypertension, active ischemia, reduced ventricular function, prior CABG surgery, class III and IV angina status before PTCA. All of these clinical descriptors were correlated with an increased risk of in-hospital death and late death by univariate analysis. Killen et al.[12] noted five univariate correlates of in-house mortality rate: emergency coronary bypass surgery, intractable cardiac arrest before ECAB, multivessel disease, prior coronary bypass surgery, and preoperative cardiogenic shock. Their data correlate well with the current report and emphasize a high incidence of severe hemodynamic collapse associated with the acute closure syndrome after PTCA and thus the need for immediately available surgical backup.

The only univariate ($p < 0.0001$) and multivariate ($p < 0.001$) correlate of both nonfatal myocardial infarction or in-hospital death in the current report was the presence of active ischemia at the time of ECAB. This factor corresponds to and likely produced the events of hemodynamic collapse described in Killen et al.'s report.[12]

In a report from the Mayo Clinic,[13] of 145 patients who required ECAB within 1 hour after ECAB, 62% had active ischemia or continuing angina and 23% were hemodynamically unstable, requiring inotropic drug or IABP support. All the deaths (2.7%) were from the latter group, and 39% had a new Q-MI. They did not observe any difference related to SVD or MVD.

A report has been published from the Cleveland Clinic in which they analyzed 198 patients who experienced failure of PTCA out of a total of 2677 elective PTCA procedures.[14] This patient population and results parallel those seen in our second 3-year cohort. Of particular interest in this report, however, are 68 of the 198 that were managed medically after failed PTCA. Why some patients were relegated to medical therapy is not clarified, but it is suggested that they were generally older with more coronary disease. Compared with the surgical group, the medically treated group experienced a higher acute mortality rate, 3% *versus* 6%, and a higher late mortality rate at 4 years, 1% *versus* 4%. In addition, 24% of the medically treated group required late CABG or repeat PTCA, which was a far higher rate than observed in their surgically treated patients and in those treated with ECAB in our report as well. This poorer outcome with medical treatment emphasized the serious late hazards related to an unsuccessful PTCA procedure and the benefit of surgical revascularization.

Even though there is a higher hospital death rate in the more recent 3-year cohort, it is interesting that fewer of them presented to ECAB with refractory myocardial ischemia than did those in the first 3-year cohort, $p = 0.0002$. This may seem contradictory. However, the preponderance of SVD patients in the first cohort produced a high incidence of acute ischemia when acute closure occurred due to the lack of collateral vessels in SVD, in comparison with the more extensive collateral vasculature often present in MVD. It follows then that once the acute myocardial ischemia is corrected by ECAB, this younger group with less negative risk factors should rebound more quickly with low operative mortality rate. In contrast, even though fewer MVD patients presented with acute refractory ischemia, the ECAB required a more extensive procedure with more grafts per patient, and their incidence

TABLE 6. *Surgical Results Analyzed by Year of Emergency Bypass Surgery*

Surgery	1980–1983	1984–1987	1988–1990	p
Grafts (mean)	1.8 ± 7	2.1 ± 1	2.2 ± 1	< 0.0001
Ischemia	27%	16%	11%	0.0002
Intra-aortic balloon pump	14%	14%	19%	NS
Q-wave myocardial infarction	18.7%	20%	14%	NS
Death	0.5%	2.4%	7.1%	0.0008

NS, not significant.

TABLE 7. *Univariate and Multivariate Correlates of Hospital Death*

	Univariate			Multivariate	
	N	Rate	p	p	χ^2
SVD	422	1.4	0.0007	< 0.001	11.26
MVD	267	6.0			
Operative Year					
Early	186	0.5	0.0008	0.051	3.80
Mid	322	2.4			
Recent	169	7.1			

SVD, single vessel disease; MVD, multivessel disease.

of Q-MI and need for IABP was the same. It was observed that when these older patients died, they often had recovered their cardiac stability with ECAB, only to die later of complications in other systems due to insults related to the ischemic episode. This higher rate of hospital mortality was not observed in other reports, which have focused on the earlier years of ECAB for failed PTCA.[12–15]

Ischemia Status at ECAB

Careful analysis of those patients presenting for ECAB disclosed no clinical descriptors that could predict the occurrence of acute closure producing refractory ischemia at PTCA. Ischemia status at ECAB, however, was a strong predictor of periprocedural Q-MI, need for IABP, prolonged hospital stay, hospital death, and a less favorable 5-year survival. There remains a controversy as to how persistent the interventional cardiology team should be in trying to correct the acute ischemia. Prolonged efforts in the catheterization laboratory to reopen a closed vessel by more dilatation efforts, placement of stents, infusion therapy, etc., can result in delaying the benefits that can be obtained by prompt ECAB. Such delays are often to no avail and can result in the ECAB being performed in the face of an established myocardial infarction rather than just acute ischemia. Our surgeons would prefer to have the patient be moved promptly to ECAB if early angiocatheter efforts are unsuccessful. Having only the catheter guide wire remain across an acutely closed area has been seen often to allow enough coronary blood flow to stabilize a hemodynamically compromised patient. The patient then can have a more orderly conduction of ECAB, even though some degree of ischemia may still be present. We have had a similar beneficial result with an autoperfusion catheter spanning the injured zone.[6] Intraluminal stents[5] when they can be placed quickly and successfully have been of dramatic effect in improving acute ischemia. However, their placement can be costly in time and is frequently unsuccessful even with insertion attempts by skilled personnel. Stents when successful may avoid the need for ECAB, especially if a small zone of myocardium is at jeopardy. However, this judgment needs to be carefully studied because the early and late problems with stents and their need for permanent anticoagulation are significant.[16]

TABLE 8. *Univariate Correlation of Hospital Death*

Univariate	N	Present/Absent (%)	p
Ischemia	533	3.7/0.8	0.09
Diabetes	100	6.0/2.7	0.07
PTCA ≥ 2 vessels	31	11.4/2.7	0.004
Ejection fraction < 50%	74	8.1/3.2	0.047
CL III–IV	18	4.0/0.6	0.08
Prior coronary artery bypass graft	4	6.8/2.8	0.9

PTCA, percutaneous transluminal coronary angioplasty; CL, Canadian Cardiovascular Society Classification.

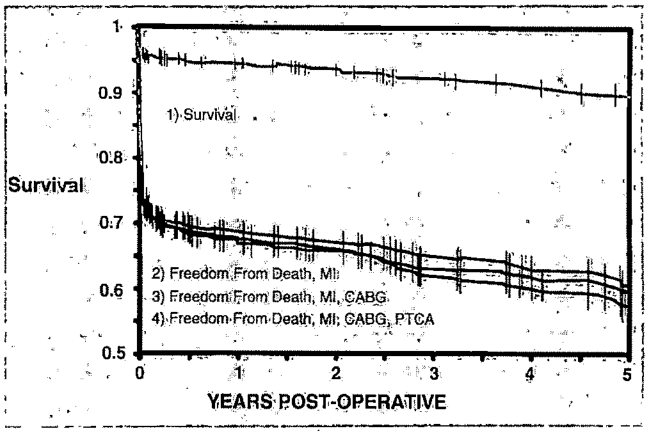

FIG. 1. Actuarial curves showing freedom from death, myocardial infarction, repeat bypass surgery, or subsequent PTCA.

Multivessel Disease

There was demonstrated an increased incidence of clinical descriptors that adversely effect operative risks in patients with MVD compared with SVD. These included

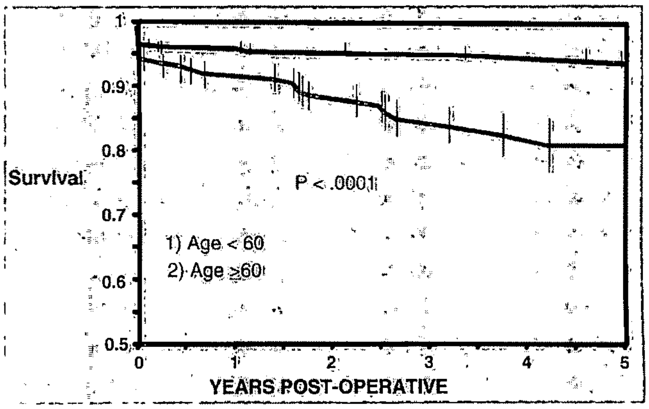

FIG. 2. Actuarial curves for late survival disease by age at time of emergency bypass surgery.

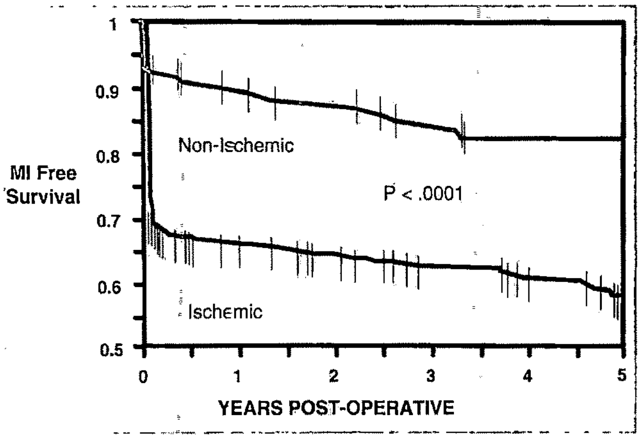

FIG. 3. Actuarial curves showing survival free from myocardial infarction analyzed by the presence or absence of acute ischemia at the time of emergency bypass surgery.

age older than 60 years, prior Q-MI, diabetes, reduced ejection fraction and multisite PTCA. All were significantly higher in MVD than SVD. Although each worked independently in univariate analysis to increase the risk of hospital death, only MVD and the more recent 3-year cohort proved valid as multivariate correlates of in-hospital death. The presence of MVD alone was the single strongest marker (univariate $p = 0.0007$ and multivariate $p = 0.001$) for in-hospital death. One would surmise that the presence of MVD in the heart circulation makes it likely that there is advanced vascular disease throughout the patient in general. This then can help explain the increased incidence of other clinical descriptors having a negative effect and the observation of cardiac recovery, but with death due to another system's failure.

The data demonstrate that the factors of multivessel disease, age older than 60 years, and active ischemia at ECAB work in concert to produce the highest risk of in-hospital death.

Late Survival

The 5-year actuarial survival was found to be affected most strongly by the patient's age older than 60 years at time of ECAB (univariate $p < 0.0001$ and multivariate $p < 0.001$). The presence of MVD *versus* SVD was correlated with less favorable survival. Other factors and year of ECAB, diabetes, congestive heart failure, and reduced ejection fraction worked actively but only in a univariate correlation and at a lesser degree of significance.

The 5-year survival and event-free rates for this population who required ECAB compares well with a study reported by Weintraub et al[17] of patients with two-vessel disease who had PTCA or CABG surgery as primary revascularization. In this study, they observed a 5-year survival of 0.94; myocardial infarction (MI)-free survival, 0.82; MI and late CABG-free survival 0.71; and MI, CABG, and repeat PTCA-free survival 0.49 after revascularization by PTCA alone. The data for primary surgical revascularization were: 5-year survival 0.89, MI-free survival 0.81, MI- and CABG-free survival 0.79, and MI-, CABG-, repeat PTCA-free survival 0.74. The multivariate correlation of advanced age, prior Q-MI, and presence of congestive heart failure, which occurred at significantly higher rates in the surgical group, resulted in 5-year survival and Q-MI–free survival curves that are superimposable for PTCA and the surgical groups. The PTCA group, however, had a much greater incidence of late events, CABG, and repeat PTCA. These data on primary revascularization for double-vessel disease patients are seen to be similar to those seen in our patients who require ECAB after PTCA, except that the incidence of Q-MI was much higher with the infarctions clustered around the initial PTCA and ECAB procedures. Emergency coronary artery bypass was not seen in the current report to have adversely effected the 5-year survival, but was shown to have substantially poorer late event-free curves when compared with elective surgical revascularization.

TABLE 9. *Univariate and Multivariate Correlates of Late Survival*

	Univariate			Multivariate	
	5-yr Survival	p	χ^2	p	χ^2
Age					
< 60 yr	0.94	< 0.0001	45.6	< 0.001	45.6
≥ 60 yr	0.81				
SVD	0.93	0.024	5.08	0.047	3.94
MVD	0.87				
Year					
Early	0.94	0.007	7.09	NS	—
Mid	0.92				
Diabetes ±	0.84/0.92	0.054	3.70	NS	—
Ejection fraction < 0.5/> 0.5	0.77/0.90	0.078	3.11	NS	—
Congestive heart failure ±	0.82/0.91	0.046	—	—	—

SVD, single vessel disease; MVD, multivessel disease; NS, not significant.

The current data after ECAB correlated well with that presented by Weintraub et al.[17] for primary PTCA. This was in contrast to a report from the Mayo Clinic in which patients who require ECAB after PTCA had 5-year cumulative risks of recurrence of angina and need for additional procedures (PTCA or CABG) that were significantly lower ($p < 0.05$) than for patients who had successful PTCA.[13] Cumulative risks of death and Q-MI were also better in patients who had undergone ECAB. The differences were concentrated in the early years after procedure and related to MVD and most strongly to incomplete revascularization. Talley et al.[15] compared the late results after ECAB post-PTCA with those observed in the randomized portion of the Coronary Artery Surgical Study. They concluded that the 5-year results obtained compared well with the CASS results of elective surgery despite the failed PTCA procedure if the patient had undergone prompt ECAB and did not develop a Q-MI. Our current study would support their conclusion and yet would recommend caution in undertaking PTCA in patients with multivessel disease and advanced age. The ability to rescue that group with ECAB and obtain a result that compares with those of primary surgical revascularization appear limited.[18] Talley et al. observed that the required ECAB after failed PTCA, if Q-MI does not occur, has a minimal negative effect on long-term survival.[15]

The increasing mortality rate and lower survival rate seen in patients with MVD and advanced age recalls an editorial statement by Friesinger[19]: "The elements needed to achieve an excellent outcome for failed PTCA in elective patients includes careful patient selection, experienced high volume operators, and readily available expert surgical backup." Although the results presented in this report are considered still quite satisfactory and the incidence of serious problems "acceptably" low, one must wonder if these can be duplicated in the PTCA practice at large.[20,21] The trend in PTCA procedures and practice seems to be that of dispersion with more and more complex patients[22] being treated by PTCA in smaller hospitals by operators who are less experienced and perform PTCA much less frequently than those whose work and results appear in the literature.[23] With the documented increased mortality rate and risk of ECAB as well as the other complication of PTCA (femoral artery hemorrhage and false aneurysm, cardiac perforation and tamponade, stroke, sudden death, etc.), one must query as to whether many of these elective patients would not be better off with medical treatment alone or elective surgical coronary revascularization. The trend to push application of PTCA for more difficult cases certainly warrants rethinking of Fresinger's admonition about patient selection and who should be doing the procedure. The randomized trials[24] currently underway in many centers (EAST, BARI, CABRI, GABI, and RITA) may help address this issue. They will still reflect the experience of major medical centers, however, and not that of the medical community at large. Whether results obtained in such centers can be extrapolated to recommend guidelines for the PTCA practice at large is quite uncertain. The current data are clear that if PTCA is to be done, immediate and skillful surgical backup is essential. Emergency coronary bypass surgery can be expected to provide rescue with excellent early and lasting results in this often desperately ill subset of patients after PTCA.

Summary and Conclusion

A 10-year experience with emergency bypass surgery support in 699 patients after failed elective PTCA is presented and analyzed in detail. The overall operative mortality rate was 3.1%, incidence of new Q wave MI 18%, and actuarial 5-year survival, 91%.

Therefore the authors conclude that:

(1) Emergency coronary artery bypass has proven successful in rescuing patients who experience acute closure after elective coronary angioplasty.
(2) Emergency coronary artery bypass has been performed with a low operative mortality rate; however, the most recent 3-year cohort has had an increased mortality rate due to increased patient age and less favorable clinical characteristics.
(3) The late results of this 10-year experience show the benefits of emergency bypass are excellent and further, these patients have rare need for additional interventional therapy or subsequent bypass surgery.

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DISCUSSION

DR. IRVING L. KRON (Charlottesville, Virginia): Dr. Ochsner, Dr. Jones, Members and Guests, I appreciate the opportunity to discuss this excellent paper. Dr. Craver and his group at Emory have clearly been leaders in new techniques and technology regarding coronary revascularization. Their results for salvaging patients after failed angioplasty are the gold standard in the field today. I looked up our own results, and my mortality rate over the last 2 years for isolated coronary revascularization, taking all comers, including redo, runs 1.2%. Emergency bypass, however, for catheter laboratory failures in our group has a mortality rate of about 5%, and we have not been able to reduce it. Deaths often are not related to cardiac failure. Frequently, the problems that occur are related to failure of other organ systems due to the hypotensive episode. In some ways, Dr. Craver's results really are a disservice to us. It has given their cardiologists the confidence to approach and perform angioplasty in settings in which most of us would prefer to perform operative revascularization. I have several questions of Dr. Craver that I think will help us all in this area. The first question deals with the use of conduits. Most of us prefer to use multiple internal mammary bypasses for the elective case. I was wondering if Dr. Craver would use internal mammaries in these acute settings. Second, I noticed that his group does not provide specific backup in the operating room for angioplasties. We agree with this, but we have noticed in our own group that atherectomies seem to have a higher failure rate. Does Dr. Craver and his group back up atherectomies, specifically?

Finally, I would like his thoughts on what those new devices such as stents and laser angioplasty have done to the rate of emergency bypass and to the results of emergency bypass. My bias is that this new aggressive approach markedly increases the risk to the patient and possibly increases the risk of emergency surgery. Again, I appreciate the opportunity to discuss this excellent paper.

DR. W. RANDOLPH CHITWOOD, JR. (Greenville, North Carolina): Dr. Ochsner, Dr. Jones, Members and Guests, Dr. Craver and his colleagues are to be complimented for the excellent results achieved at Emory University in patients undergoing emergency coronary surgery after failed elective percutaneous angioplasty. They have emphasized that although coronary angioplasty has revolutionized the treatment of coronary artery disease, the method is far from a panacea. Coronary surgeons are now presented with an often difficult controlled emergency. Dr. Craver's superb review reflects data from more than 12,000 elective angioplasties at Emory over the past decade. Of these patients, 5.8% required emergency coronary surgery after angioplasty failure; and 82% had ongoing ischemia during transport to the operating room. The overall surgical mortality for these patients was low, at 3.1%. Dr. Craver has shown, however, that this trend is changing. Even though surgeons are now able to stabilize patients after angioplasty failure, the patient population having angioplasties has changed markedly, with emergency surgery becoming much higher risk because of increasing age and concurrent medical problems. Although a much smaller series, we have experienced similar problems and results. Our center at East Carolina University began coronary angioplasty in 1985, and during the past 2 years performed 1550 angioplasties. Of these, 2.5% underwent emergency coronary surgery, and 46% of this group was older than 60 years of age.

On arrival in the operating room, 69% had ongoing ischemia, with 38% stabilized by an intra-aortic balloon pump. In comparison, 31% had coronary blood flow reestablished in the catheterization laboratory with a perfusion or bailout catheter and were very stable on arrival in the operating room, with most receiving an internal mammary artery graft. There were two operative deaths for a 5.1% mortality rate, with both deaths being in the ischemic group.

Dr. Craver, I congratulate you on your study and thank you for this valuable information. I have a couple of questions for you. Firstly, at Emory, what has been the role of cardiopulmonary support in stabilizing patients in the catheterization laboratory, as well as standing by patients for high-risk angioplasty? Do you ever put patients on cardiopulmonary support in the catheterization laboratory? Also, what are your current recommendations for a surgical standby in a moderate-sized cardiac surgical program? And, lastly, do you take down the internal mammary on cardiopulmonary bypass when these patients are very ill from a failed angioplasty? As a new member of the Association, I would like to thank the Association for the privilege of discussing this very nice paper. Thank you.

PRESIDENT OCHSNER: I also would like to ask you a question. You said you were unable to identify any factors that were referable to the incidence of failed percutaneous transluminal coronary angioplasty. How about the expertise of the individual angiographer, did you look at that, or do you have any information on that?

DR. JOSEPH M. CRAVER (Closing discussion): I would like to thank the Association for the opportunity to present the paper and my friends Irv Kron and Randy Chitwood for bringing up these discussion points. Irv, to speak to your items first. I think we can expect a higher mortality rate in patients who come for emergency bypass because of the things that we mentioned. First, this is a less favorable group of patients; they are older, and the angioplasty physicians are becoming increasingly aggressive. With increasing numbers of hospitals offering angioplasty, there will be more angioplasties done by more operators, so there will be fewer angioplasties per angioplasty physician. And I think the degree of expertise will go down as time passes.

You and Randy both mention the use internal mammary arteries for emergency bypass conduits. We tend to gauge that according to the stability of the patient when he arrives in the operating room. If they are stable, if the anesthesia induction and the hemodynamics go satisfactorily, and we can get them on bypass; then the internal mammary artery is taken down on bypass and used. Our guiding principle, however, is to restore blood flow into the ischemic area promptly and as effectively as possible. So those patients who have continuing ischemia, who have hyperacute EKG changes still present, or who are in any shock form get a vein graft into the injured vessel, left anterior descending, right, or wherever, and we get out of there as quickly as we can with the perfused myocardium. Our surgical backup is the same for angioplasty and for atherectomy. The incidence of angioplasty having a problem is higher in our center than atherectomy, although atherectomies do develop problems. Not infrequently the patients who are having an atherectomy have a balloon at the same time, so they convert into the same group. The atherectomy patients have a higher incidence of restenosis down the line as a late problem. But I think overall atherectomy does not entail the same problem of producing a dissection or an acute closure, as we have seen with balloon angioplasty. The presence and the developing expertise of the angioplasty people in using intracoronary stents and bailout catheters is one of the reasons we have fewer patients arriving in an acutely ischemic state than we did in the first 3 years of our experience. In addition to less acute myocardial ischemia just leaving the guiding wire across the injured lesion tends to keep the dissection flap from completely closing. So it does not take much blood flow to stabilize the acute ischemia. Once you then get the patients on bypass, the major myocardial protection becomes reducing the load on the heart by the bypass, by cardioplegia techniques that, it is hoped, can return some nutrients and oxygen to the area, allowing for a prompt revascularization and normal blood flow reestablishment.

I think the report on laser therapy strategies is still out. We do not as surgeons have a great deal of enthusiasm for that modality being used in the coronaries because of the small size, tortuosity, and mobility of the coronaries. Also in our hospital the laser is used as a channel creator to open an avenue for placement of the PHA balloon. A major problem that we have had with these laser stents, and intracoronary devices is the delay getting a patient who's experiencing acute ischemia from the catheterization laboratory suite to the operating room. We believe if we can get them to surgery, get them on bypass, and get them revascularized, we can do that with about a half-percent mortality rate. If, however, there's a 2- or 3-hour delay while the fellows or the catheterization laboratory personnel try to get in a stent, not infrequently the myocardial ischemia becomes firmly established. The surgeon is then operating on a person with an infarction as opposed to a person with acute ischemia. That has contributed significantly in the last 3 years to the increased mortality rate of those patients here.

Randy, I would think that angioplasty has changed coronary atherosclerotic heart disease treatment rather than revolutionized it. I think revolution implies an improvement. The only thing it has done is taken the scars off people's chests. Our group looked up about 1500 consecutive patients in the early 1980s that would correlate to the angioplasty group. We operated on those patients with a 0.2% mortality rate with a 96% survival rate at 5 years. Now angioplasty does not come anywhere near that. So it has not revolutionized it, but it has taken the scars off of a substantial number of patients. Not infrequently, however, angioplasty has to be done multiple times, as you well know. We have not been enthusiastic about supporting the difficult angioplasty patients with cardiopulmonary bypass in the catheterization laboratory. I think that is intrinsically unsound. We would rather have those patients referred for surgery and do a proper operation. Occasionally, there will be somebody we do not think is a candidate, and we have stood by but have not used it yet. This is in contrast to some other people's experience, which we're interested in following. I thank you again for the opportunity to talk.

Infected Aortic Aneurysms

A Changing Entity

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Infected (mycotic) aortic aneurysms are infrequent and, without surgical intervention, usually lead to uncontrolled sepsis or catastrophic hemorrhage. Symptoms are frequently absent or nonspecific during the early stages, and a high index of suspicion is essential to make the diagnosis. Surgery performed after rupture carries high morbidity and mortality rates. Bacterial endocarditis with streptococcus pyogenes was the most common cause of infected aortic aneurysm in the pre-antibiotic era. Today, arterial trauma due to iatrogenic manipulation and depressed immunocompetence have become more common risk factors. *Staphylococcus aureus* and *Salmonella* are the most frequent bacteria identified. The authors' recent experience in six patients with infected aortic aneurysms who underwent arteriography and computed tomography was reviewed and these diagnostic methods compared. Computed tomography was found to be more sensitive in the diagnosis of the early stages of the disease, allowing for follow-up by serial scans in a noninvasive and less costly manner. Successful treatment, in four of these patients, was accomplished by aneurysmal resection and extra-anatomic bypass or *in situ* prosthetic reconstruction. A higher clinical awareness of this disease, leading to early computed tomography evaluation and prompt surgical intervention under appropriate and intensive antibiotic therapy, appears to offer the best chance of survival in patients with this difficult condition.

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A CENTURY HAS passed since the classic report of Sir William Osler[1] to the Royal College of Physicians in the landmark Gulstonian Lecture in London in 1885 on "malignant endocarditis" in which he described the pathophysiology and introduced the term of mycotic aneurysms. He evaluated the relationship between the presence of aortic valve vegetations in a single patient and four aneurysms of the aortic arch that had the "appearance of fresh fungus vegetations" on their internal surface. The patient was a 30-year old man admitted with chills, fever, and pneumonia who developed bacterial endocarditis and eventually died of aneurysmal rupture. Osler deduced that embolization of these organisms to a peripheral vessel led to septic degeneration of the arterial wall, "mycotic aneurysm" formation and rupture. The term "mycotic aneurysm" has since been applied to arterial infections of all types, although today it is generally used more restrictively for fungal infections and, hence, the designation of infected aneurysms (IAA) is the most appropriate, as suggested by Jarrett et al.[2] Earlier reports[3] in 1844 had described the presence of abscesses in arterial walls caused by infected emboli, and Koch in 1851[4] and Tufnell in 1853[5] recorded single case reports of peripheral aneurysms occurring in young patients, in their early 20s, during treatment for endocarditis.

Most IAA in the earlier reports were associated with valvular infectious disease. This was found in 187 of the 217 cases (86%) assembled by Stengel and Wolferth in 1923.[6] The aorta was the most frequently involved artery, being affected in 66 of 217 cases. In the pre-antibiotic era, bacterial endocarditis and its complications were uniformly fatal. The development of vascular grafts and antibiotic therapy lead to the first reported survival of patients with an IAA in 1962 by Sower and Whelan[7] and Morris et al.,[8] but even as late as the 1960s and early 1970s most of the patients with this disease process died.

Newer microbiologic techniques for identifying the infecting organism and appropriate antibiotic therapy combined with successful replacement of infected valves have markedly reduced the incidence of embolomycotic aneurysms of the aorta in the United States. Occasional reports of septic emboli from bacterial endocarditis still appear in the literature, particularly in children.[9,10] This is in sharp

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contrast with the reports from the 1930s,[11] when an IAA "in the absence of valvular disease was very unusual." The term "primary mycotic aneurysm" was introduced by Crane,[11] applying it to those aneurysms occurring in the absence of overt sepsis.

In the postantibiotic era, about 80% of the infections of the aorta appear to result from microbial arteritis.[12] An increasing number of IAAs appearing because of the implantation of circulating bacteria in a diseased, atherosclerotic, or traumatized aortic intima, with wall separation and aneurysm formation have been reported in recent years. These vessels are usually already involved by acquired diseases or congenital anomalies. Another mechanism of infection is due to direct extension or through lymphatic vessels from an adjacent infectious process. Infection in a pre-existing aneurysm also can occur and is estimated to occur in 3% of aneurysms.

Several risk factors are more common now than in the past. These include diagnostic or therapeutic arterial catheterization, illicit intravascular drug use, the higher prevalence of patients with depressed immune competence secondary to either chronic or neoplastic diseases, and, since 1981, the rising number of patients with acquired immune deficiency syndrome.

Changes in the diagnosis, causes, risk factors, natural history, and treatment of IAA prompted us to review our recent surgical experience.

Case Reports

During the period between 1986 and 1991, six patients were evaluated and underwent resection of IAAs. The clinical and diagnostic findings as well as the surgical procedures and outcome are summarized in Table 1. The three men and three women were 61 to 75 years of age (mean, 68.7). Two of the aneurysms involved the descending thoracic aorta, and both patients complained of prominent chest pain. The remaining four involved the abdominal aorta, three located in the infrarenal segment and one supraceliac. Abdominal, flank, or back pain were present in all instances.

Predisposing conditions included diabetes mellitus in three patients, atherosclerosis in four patients, and rheumatoid arthritis and carcinoma of the bladder in individual cases.

All patients had evidence of sepsis with fever, leukocytosis, and, in three of them, positive blood cultures (two salmonella species and one *Staphylococcus aureus*). Salmonella was also identified by a computed tomography (CT)-guided needle biopsy of a para-aortic mass in another patient. These organisms were confirmed also by cultures of the aneurysm wall at the time of the resection; in the remaining two patients, *Listeria monocytogenes* and a Staphylococcus species were the infecting organisms isolated from the wall of the aneurysm. Both of these patients had undergone prior antibiotic therapy. Pre-existing sepsis was documented in one patient with urinary tract infection, another with colonic diverticulitis, and in two with Salmonella enterocolitis.

In no instance was the aneurysm diagnosed on a clinical basis alone. A plain lateral chest radiograph suggested the diagnosis of a descending thoracic aneurysm that was confirmed by CT scanning and angiography in one patient. The other thoracic aneurysm was known to be present for the past 5 years from the time of an exclusion procedure performed in another hospital for an acute dissecting aneurysm with ligation and division of the aorta proximal to the origin of the left subclavian artery

TABLE 1. *Summary of Findings*

Age	Sex	Location of Aneurysm	Associated Conditions	Symptoms/Signs	Organism	Angiograph	Computed Tomography	Surgery	Outcome
72 (1986)	M	Descending thoracic	Atherosclerosis, rheumatoid arthritis	Fever, leukocytosis, recurrent chest pain	*S. pneumonia*	Saccular TAA (3 cm)	Periaortic mass saccular TAA	*In situ* graft	Alive at 5 yr
75 (1986)	M	Supraceliac	Atherosclerosis, diverticulosis	Fever, leukocytosis, abdominal pain, diarrhea	*L. monocytogenes*	Saccular AAA (11 × 8 cm)	Saccular AAA (4.5 cm) 10 days, saccular AAA (8 cm)	*In situ* graft	Alive 2.5 yr
66 (1988)	M	Infrarenal	Atherosclerosis, diabetes, cancer of the bladder	Fever, leukocytosis, flank pain, urinary infection	*S. aureus*	Not done	Periaortic mass, saccular AAA	Drainage abscess, Ax-fem, fem-fem	Died (6 wk), sepsis
70 (1989)	M	Infrarenal	Atherosclerosis, salmonellosis	Fever, leukocytosis, back pain	Salmonella	Refused	Saccular AAA (2 cm) 3 mo, saccular AAA (5.5 cm)	Ax-fem, fem-fem	Died (4 mo), sepsis
68 (1991)	F	Distal abdominal	Diabetes	Fever, leukocytosis, lower abdominal pain	Salmonella	Bilobar saccular AAA	Periaortic mass	Ax-fem, fem-fem	Alive
61 (1991)	F	Descending thoracic	Diabetes, salmonellosis	Fever, leukocytosis, chest pain	Salmonella	Excluded TAA, patent subclavian artery	Perianeurysmal mass	Resection TAA	Alive

and at the distal thoracic level with an ascending aorta to abdominal aorta bypass. The plain film showed a large mediastinal mass that appeared unchanged over the period of observation.

Saccular aneurysms were visualized in three of the patients angiographically (Figs. 1 and 2); in another the left subclavian artery and its origin were seen arising from the excluded thoracic aneurysm. Angiography was refused by one patient and was not performed in the remaining patient because he was seriously ill and underwent surgery based on the CT findings alone.

The CT findings were diagnostic in all six cases. A periaortic soft tissue mass with rim enhancement was seen in three patients; one around a calcified aorta of normal size (Fig. 3A), another around a 3-cm saccular aneurysm, and the last around a large thrombosed, descending aortic aneurysm. Expansion of the soft tissue mass 2 weeks later in the first patient prompted a CT-guided needle aspiration (Fig. 3B). Saccular aneurysms were visualized in the three remaining patients, two of which increased significantly in diameter during the period of observation, from 4.5 to 8 cm over a 10-day interval in one patient and from 2 to 5.5 cm in a 3-month period in another (Figs. 4A and B). Aortic calcification was clearly visible on CTs in four patients in this series.

All patients were treated with the appropriate antibiotics and underwent aneurysmal resection with debridement of the periaortic infected soft tissue. A large defect in the aortic wall was present in two cases, and one of these patients had a periaortic abscess that was drained posteriorly. Extra-anatomic bypasses (axillary–bifemoral) were performed in three patients and interposition grafts in two. The left subclavian artery was ligated at its origin with the resection of the descending thoracic aneurysm in the remaining patient; a graft from the left carotid to the left subclavian artery had been constructed at the time of the original aorto-aorto bypass and aneurysmal exclusion and was patent.

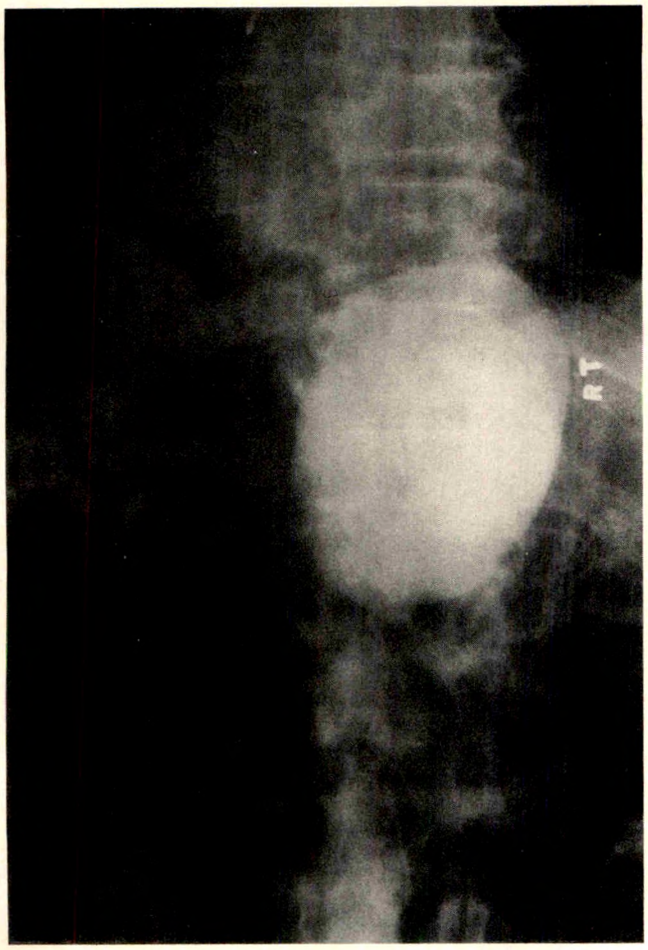

FIG. 1. Anteroposterior projection of retrograde brachial aortogram showing a large, saccular, 8-cm, supraceliac aortic aneurysm (case 2).

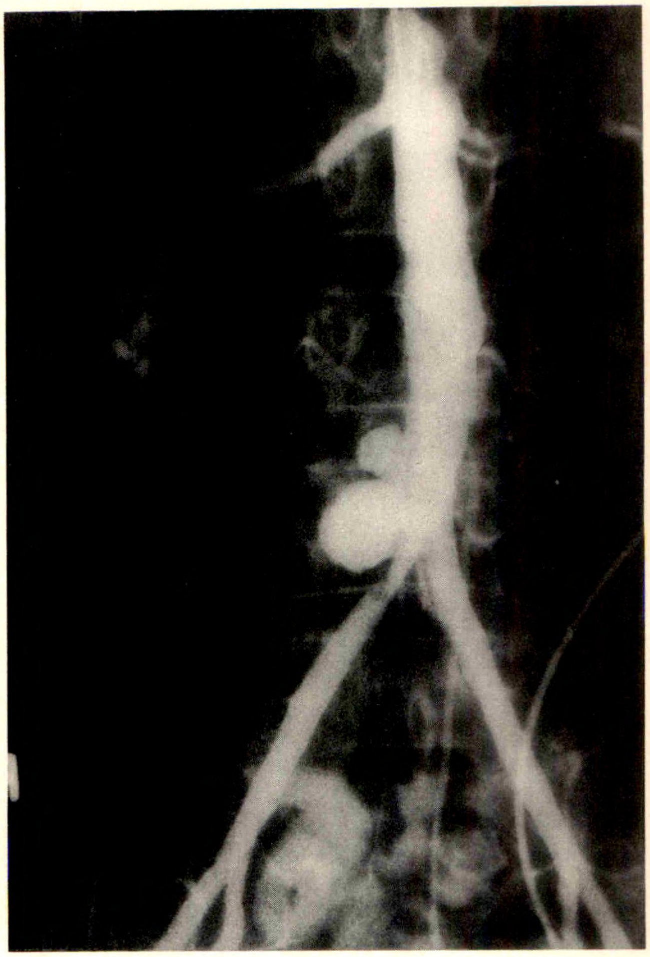

FIG. 2. Transfemoral arteriogram shows atypical aortic aneurysms originating at the distal abdominal aorta (case 5).

The overall mortality rate was 33.3% (two of six patients), one 6 weeks and the other 4 months after surgery because of generalized sepsis. Both of these patients had extensive periaortic infection, with necrosis of the aortic wall and preoperative septicemia with positive cultures of the urine and stool. Extra-anatomic bypass grafts were the operative procedures in these two patients: the inability to debride all infected tissue also may have contributed to the late postoperative deaths in spite of the initial successful surgical results.

Discussion

Infected aortic aneurysms are uncommon but not rare as our experience of six cases in a 5-year period in one institution suggests. Other authors[13] have also identified an increasing number of these aneurysms in recent years, suggesting that its incidence may be increasing.

The nature of IAAs is changing. Bacterial endocarditis was not the cause of the infection in any of our six patients.

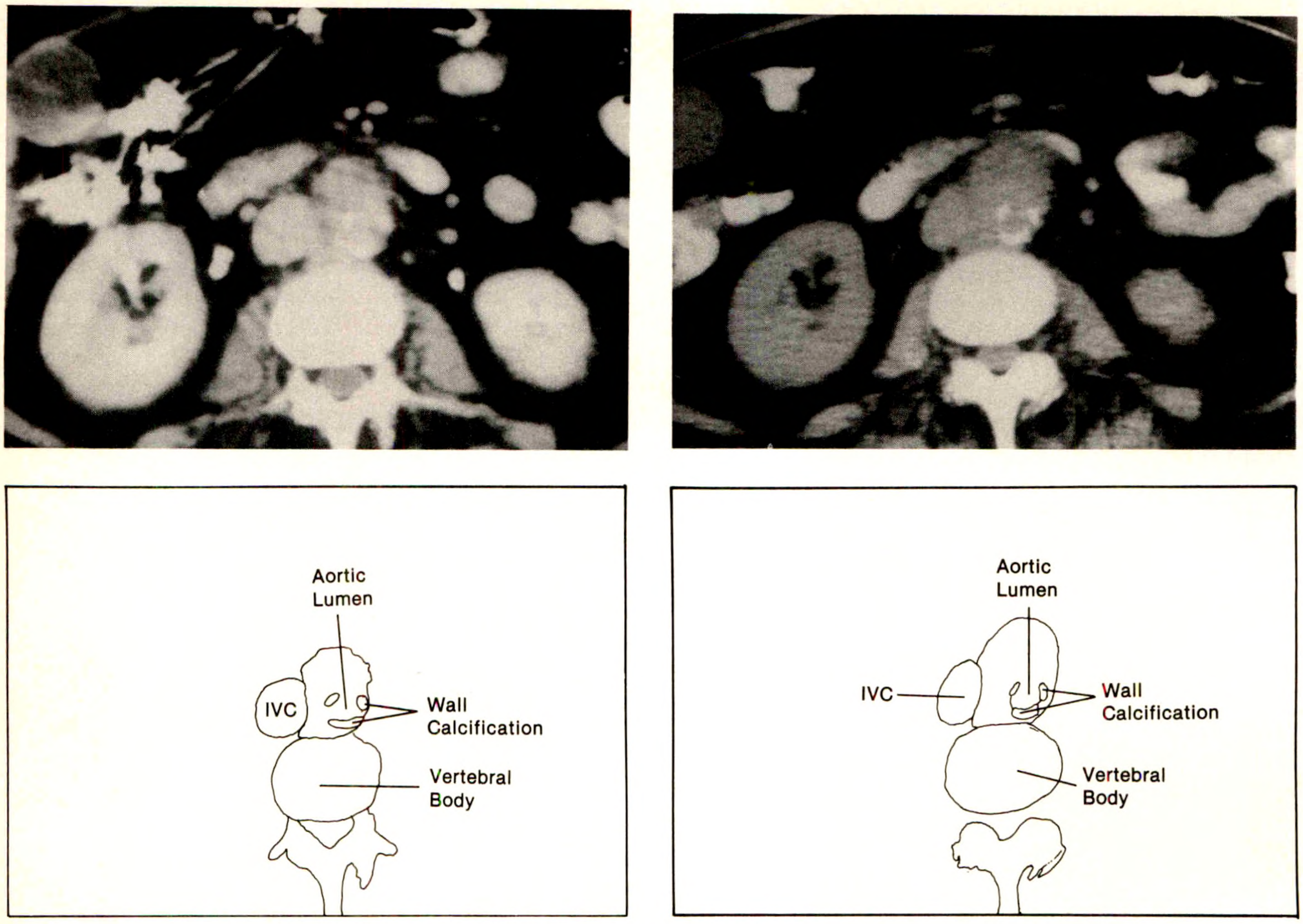

FIG. 3. (A, left) CT scan shows a calcified infrarenal aorta of normal size with an irregular, anterior, soft tissue mass inseparable from the aorta. (B, right) Repeat CT scan 1 week later shows significant enlargement of the soft tissue mass (case 5).

In our review of 19 reports in the English literature involving 28 patients with IAAs (from 1983 to 1991), the findings were similar except for three pediatric patients, in whom embolomycotic aneurysm of the abdominal aorta developed.[9,14] With few exceptions, all of the reviewed reports were of single cases or of small series. In a larger 15-year cumulative review (1968 through 1982), Johansen and Devin[15] found bacterial endocarditis to be a risk factor in only 17% of 220 patients, although they emphasized that most of this subgroup of patients appeared in reports from the British Commonwealth.

The mean age of our patients (68.7 years) is slightly higher than in our reviewed group (mean, 61.2 years), if the three pediatric cases are excluded. This trend toward older age is apparent when earlier series of IAAs are reviewed such as in a collected series by Wilson et al.[16] from the 1960s, in which the mean age for aneurysm secondary to bacterial endocarditis was 26 years.

The *bacteriology* of these infections appears also to have changed. In the pre-antibiotic era, the predominant organisms were *Streptococcus pyogenes, S. pneumoniae,* and staphylococci,[6] whereas in the postantibiotic era the dominant infecting organisms are the *Staphylococcus aureus* and the Salmonella species,[17] accounting for about 40% of the total organisms cultured. Our experience confirms this, these bacteria being identified in four of the six patients. It appears that the presence of atherosclerosis, with or without aneurysmal changes, makes the aorta more susceptible to the development of salmonella endovascular infection, but even the normal arterial intima, usually resistant to bacterial entrance, may be invaded by Salmonella.[18] Given the high prevalence of untreated salmonella gastroenteritis preceding endothelial infection, some authors[19] advise antibiotic therapy for its treatment in patients older than 50 years of age. A tendency toward an early rupture has been noted in the cases due to Salmonella infection.[20]

Reports of other less common organisms are starting to appear in the literature and may reflect the presence of immunocompromised hosts. *Listeria monocytogenes,* for instance, has been incriminated twice as the cause of IAAs[21] and was seen in one of our six patients. A poten-

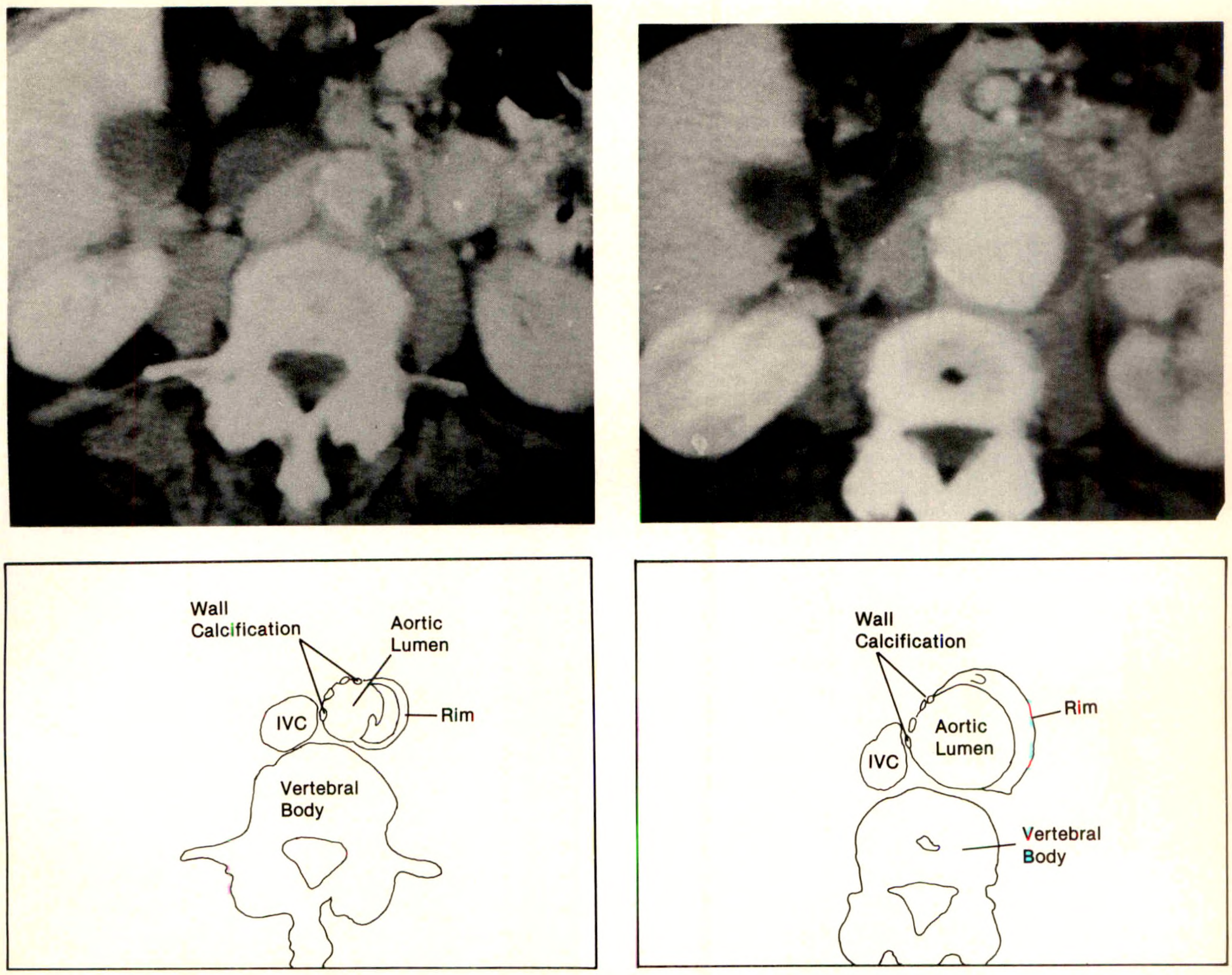

FIG. 4. (A, left) Contrast-enhanced CT scan shows an irregular periaortic soft tissue mass with peripheral enhancement consistent with inflammation. (B, right) CT scan 3 months later shows a sharp increase in the diameter of the aortic lumen (case 4).

tially large and increasing number of immunocompromised patients due to acquired immune deficiency syndrome is another at risk population for IAA. In the past year, three cases of an IAA have been reported in male patients with a positive test for the human immunodeficiency virus. No organisms were cultured from the aneurysmal contents in one of the patients, but *Salmonella* and *Mycobacterium tuberculosis* grew in the two others. These numbers could dramatically change in the near future.

Bacteroides fragilis, an anaerobic organism, has been reported[22,23] as the causative agent of IAA. Although these cases appear to be rare, it is possible that the incidence is higher than reported because negative cultures from IAAs have been stated to be found in as many as 25% of cases,[12] and this may reflect the fact that the anaerobic cultures may not be routinely obtained. The frequent use of antibiotics in general medical and surgical practice is another likely reason for the high percentage of failures in identifying a specific pathogen.

Campylobacter fetus has a particular predilection for the vascular endothelium in immunocompromised patients and, since 1971, nine documented cases of *C. fetus* sepsis associated with abdominal aortic aneurysms have been reported.[24] Rapid increase in the size of the aneurysm is found with this entity, and all the reported deaths in this series followed aneurysmal rupture.

Overall, gram-negative infections have shown a greater virulence with a significantly higher incidence of aneurysmal rupture and death (72% *versus* 25%) than aneurysms with gram-positive infections.[20]

Analysis of the associated conditions present in our group of patients showed that diabetes mellitus, malignant neoplasm, and rheumatoid arthritis were present, alone or in combination, in four of them, indicating compromised immunocompetence. Johansen and Devin[15] found depressed host immunity due to chronic alcoholism, administration of corticosteroids or cytotoxic agents, and chronic renal failure present in 24% of the patients reviewed. Arterial trauma was the greatest risk factor and was present in 29%. The development of a "mycotic" aortic aneurysm after arteriography or cardiac catheterization is rare,[25,26] but given the large numbers of patients that undergo diagnostic or therapeutic (intra-aortic balloon pump, percutaneous transluminal coronary angioplasty, percutaneous balloon angioplasty, hemodialysis shunts) arterial catheterizations, one has to be aware of this possible complication. Arterial trauma secondary to parenteral drug abuse has increased markedly in recent years. Direct trauma to the vessel with contamination of the resulting hematoma during initial or subsequent injections will lead to formation of an infected pseudoaneurysm or bacterial endocarditis. Drug addicts are probably now one of the larger groups of patients with bacterial endocarditis and its potential embolic arterial complications.[27] This will no doubt worsen as acquired immune deficiency syndrome begins to affect this population.

Pre-existing or concurrent sepsis, either distant or contiguous, was present in 17% of the quoted study[15] and in four of our six patients.

Even from the analysis of our small series, it is most likely that several of these mechanisms may be present in an individual patient; nevertheless, about 3% of patients with IAA have no obvious risk factor.

Diagnosis of an IAA can be difficult. Fever and leukocytosis were present in all of our six patients, but not the remaining element of the classic triad—the pulsatile mass. An aneurysm was palpable in only 53% of cases in one series.[20] A number of cases present as fever of unknown origin with some nonspecific abdominal or chest pain and no distinctive clinical presentation. The systemic manifestations of sepsis may be discrete, and the IAA may go unrecognized, particularly in the early stages.

Positive blood cultures were found in only three of our cases, but a higher percentage (70%) has been reported.[28] Downstream arterial blood cultures from the femoral artery can be particularly helpful in the diagnosis of IAA. Traditionally, aortography is considered crucial to the diagnosis of this entity by demonstrating the presence of lobular, saccular, and eccentric aneurysms in an otherwise normal appearing aorta. Arteriography was performed in four of our patients but more for preoperative planning and confirmation of the CT findings than for diagnosis. Computed tomography scans suggested the diagnosis in all six patients. The CT features have been reported previously,[29] but early findings include the presence of a periaortic soft tissue density with rim enhancement, and intimal calcifications. Days to weeks later, this eccentric, thickened wall may increase in size, and the intimal calcifications may become disrupted or disappear. Enlargement of the aortic lumen eventually develop, which took place between 10 days and 3 months after the original scan in two of our patients; an unusual luminal shape also may be seen. Gas in the perianeurysmal soft tissue has been described.[30] The progression of a normal vessel to a markedly dilated and thinned one may be very rapid, as we and other authors[30–32] have observed.

The *surgical therapy* aims not only to eradicate the IAA and surrounding tissues, but also to re-establish distal arterial flow.

Dismal results of resection and vascular reconstruction for IAAs were described as recently as 1967.[33] All of the patients in that series died of persistent sepsis after *in situ* insertion of a graft in the infected field. Brown et al.,[12] among others, further pointed out the disadvantages of *in situ* reconstruction, where a mortality rate of 32% was found *versus* a mortality rate of 13%, when resection and extra-anatomic bypasses were performed in a similar group of patients.

Most surgeons probably consider the excision of the IAA with ligation of the aorta, drainage of the retroperitoneum, and remote bypass grafting as the treatment of choice.[22,25,34,35] In the sequence of aneurysmal rupture and widespread periaortic sepsis, this is obviously the appropriate approach. The difficulties of removing all necrotic tissue and providing adequate drainage are well recognized. The two deaths in our series secondary to late generalized sepsis were likely due to the inability to debride all adjacent infected tissue. Closure of the aortic stump is also a crucial step given the potential for late disruption in the presence of residual infection and, invariably, fatal hemorrhage. Adequate posterior drainage of the retroperitoneum is required because frequently, even after careful debridement, purulent material with the same organisms as found in the aneurysmal tissues continues to drain for variable periods.

The lower patency rates of the axillary-femoral grafts and the possibility of graft infection due to persistent or recurrent septicemia has led to the re-evaluation of the *in situ* graft interposition. Successful aneurysmal resection and graft replacement has been reported several times[15,21,24,25,36,37] in cases of IAAs after the first initial success by this method in 1962.[7] Two patients in our series were treated in this manner and were alive 2.5 and 5 years after operation. There is no uniformly accepted consensus regarding which patients should be treated by this approach. Reddy[13] describes an approach based on the results of a Gram stain obtained intraoperatively of suspicious areas of the aneurysmal wall and contents as well as the presence of gross infection. Aneurysmal resection and *in situ* graft replacement is advised for cases in which the Gram stain is negative and there is no evidence of macroscopic purulence. In the face of a positive Gram stain but no gross infection, the same surgical procedure can be cautiously done if one can be fairly certain that debridement can fully clear the retroperitoneal infection. *In situ* reconstruction is also desirable in aneurysms of the suprarenal aorta involving the visceral arteries, given the lack of any practical alternative. In a large series of patients reported by Chan et al.[38] and others,[39] the authors conclude that this is the method of choice for central mycotic aneurysms but advise lifetime oral antibiotic suppression.

A persistent fever, positive blood cultures, evidence of anastomotic breakdown, or signs of retroperitoneal sepsis should indicate the need for the placement of an extra-anatomic bypass and prompt removal of the interposed aortic prosthesis. The rate of failure of interposition grafts has been reported to be 23% with infection caused by gram-positive organisms and up to 63% with gram-negative organisms.[40] Replacement grafting is also an expedient operation when the patient is in extremis. When there is evidence of gross infection, an extra-anatomic bypass should follow the resection of the IAA and the debridement of the retroperitoneal infected tissue. Concern about prolonged leg ischemia after excision of the aneurysm followed by the extra-anatomic bypass can be allayed by reversing the order of the procedures.[35] The possible bacterial seeding of the fresh graft in the process of the resection and debridement of the IAA and retroperitoneal tissues does not appear to have practical significance.[41]

The treatment of IAA begins preoperatively with the appropriate antibiotics adjusted to the cultured organism and with effective serum antibiotic levels. Surgery should, if possible, be performed after the establishment of effective antibiotic therapy but should not be delayed beyond that time (1 to 4 days). Aggressive and appropriate antibiotic treatment must be continued after operation to accomplish sterilization of the blood stream and the operative site. There are no definite recommendations for the duration of the postoperative antibiotic therapy, but a minimum of 6 weeks has been suggested.[13] In certain cases, and depending on the method of arterial reconstruction, oral antibiotics may be required for a lifetime.[42] Late reinfections have been reported in patients who did not continue the therapy, particularly caused by Salmonella organisms.[12]

If the infection is detected early, this approach should provide a favorable outcome in most of these patients (Table 2).

TABLE 2. *Infected Aortic Aneurysms: Patient Survival*

Source	Year	No. of Cases	Survivors No. (%)
Jarrett et al.	1975	12	7 (59)
Davies et al.	1978	3	3 (100)
Scher et al.	1980	2	1 (50)
Johansen and Devin	1983	4	4 (100)
Bitseff et al.	1985	5	3 (60)
Taylor et al.	1987	4	4 (100)
Current series	1991	6	4 (66.7)

Much remains unknown about the clinical course of IAAs, but experience indicates that, although the rate of the disease progression varies widely between patients, the natural history of these processes is highly unfavorable and usually fatal because of sepsis or hemorrhage.

From our experience and the literature review, it appears that several aspects of this disease have changed over the years. These lesions appear more frequently now in an older population, although the acquired immune deficiency syndrome and drug epidemics may change the demographics of this disease in future years. The main risk factor is no longer the presence of bacterial endocarditis, and IAA will be secondary to various states of depressed immunity, infected sites of arterial trauma, and concurrent sepsis elsewhere. Computed tomography appears to provide earlier diagnosis and a good technique to follow the progress of this disease if the diagnosis is not initially made, but clinical suspicion of this entity is fundamental for its early diagnosis. Angiography provides the anatomic details of the lesion and adjacent vessels, but will not show the degree of periaortic extension that CT can demonstrate.

An early diagnosis permits the *en bloc* excision of the aneurysm and the perianeurysmal infection and allows an interposition graft, a shorter, one-stage procedure, with good long-term results. Delayed diagnosis with extensive periaortic sepsis will require ligation of the aorta and extra-anatomic bypasses. Aortic rupture continues to carry a high mortality rate.

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DISCUSSION

DR. HUGH H. TROUT III (Bethesda, Maryland): President Ochsner, Dr. Jones, Members and Guests: In situations in which contamination is likely, it now seems that it is reasonably safe to proceed with *in situ* prosthetic graft insertion when no previous prosthetic graft has been placed. Such settings include a primary aortoenteric fistula with a communication between an abdominal aorta aneurysm and the duodenum. Another instance would be infected aortic aneurysms as presented by Dr. Gomes. One other instance in which *in situ* replacement seems possible is the setting of a prosthetic graft infected by bacterial biofilms such as coagulase-negative staphylococcus, as has been recently reported. For all other vascular contamination situations in my view, however, *in situ* grafting should be avoided if at all possible. Appropriate therapy in these instances should be a remote bypass such as an axillobifemoral bypass, followed by removal of the contaminated graft.

I have one question. Now that polytetrafluoroethylene (PTFE) is available in bifurcation form, do you believe because of reduced quantitative bacterial adherence that PTFE has an advantage over Dacron as a prosthetic replacement graft? I want to thank Dr. Gomes for providing me with a copy of his excellent manuscript and to congratulate him on a thorough presentation helping to define further those instances in which *in situ* grafting may be safely employed. Thank you for the privilege of the floor.

DR. MARIO N. GOMES (Closing discussion): I would like to thank Dr. Trout for the kind comments. I do believe that the use of a PTFE graft in this setting may further decrease the possibility of graft infection, but it is more important to make the diagnosis of IAA in early phase and be fairly certain that the periaortic involvement is not present. In these circumstances, the potential problem of graft infection should not be significant, but the use of a PTFE graft may be advantageous. I am fairly confident that an early diagnosis of IAAA will lead to a safe graft interposition, which is not the case when extensive periaortic infection is present.

Juxtarenal Aortic Occlusion

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The authors' experience with 113 aortic occlusions in 103 patients during a 26-year period (1965 to 1991) is reviewed. The authors found three distinct patterns of presentation: group I (n = 26) presented with acute aortic occlusion, group II (n = 66) presented with chronic aortic occlusion, and group III (n = 21) presented with complete occlusion of an aortic graft. Perioperative mortality rates were 31%, 9%, and 4.7% for each respective group and achieved statistical significance when comparing group I with group II (p = 0.009) and group I with group III (p = 0.015). Group I presented with profound metabolic insults due to acute ischemia and fared poorly. Group II presented with chronic claudication and did well long-term. Group III presented with acute ischemia but did well because of established collateral circulation. The treatment and expected outcome of aortic occlusion depends on the cause.

> . . . . le traitement idéal consisterait évidment a resequer la zone obliterée et à retablier la permeabilitè si c'est possible . . ."
>
> R. LeRiche (deLyon) 1923

OCCLUSION OF THE juxtarenal aorta (JRA) may present as an acute vascular catastrophe, chronic lower extremity ischemia, or as an aortic graft occlusion, a sudden event superimposed on chronic atherosclerotic occlusive disease. All of these scenarios produce formidable treatment challenges because of the potentially disastrous sequence of events associated with lower extremity ischemia.

In 1923, LeRiche[1] described the condition of aortic occlusion and envisioned resection of the occluded segment as the treatment of choice. Unfortunately, he had neither the technique or the skill to see his vision to fruition. Reconstructive efforts began in 1947, when Dos Santos[2] performed abdominal aortic endarterectomy, and

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in 1950, Oudot[3] replaced the terminal aorta with an arterial homograft for chronic occlusive disease.

The ensuing years have seen numerous advances in the approach to aortic occlusion. The vascular surgeon's armamentarium is overflowing with creative solutions: embolectomy, thrombolytic therapy, and extra-anatomic bypass, using a variety of graft materials to revascularize the lower extremities.

Despite these developments, the mortality rate of acute aortic occlusion (AAO) and disability from chronic occlusion (CAO) remains significant. To better understand the presentation, management, and expected surgical outcome, we have reviewed our experience with this multifaceted disorder.

Methods

During the years 1965 to 1991, 4126 aortic reconstructions were entered in the vascular registry at St. Thomas Hospital. Abdominal aortic aneurysm was the operative indication in 1774, whereas aorto-iliac occlusive disease was found in 2352. The male/female ratio was 3:1.

One hundred three patients required 113 operations for JRA occlusion during this period. Retrospective analysis was obtained from the medical records, and follow-up was secured through clinical evaluation or phone interview. Follow-up ranged from 6 months to 24 years (mean, 5 years); no patient was lost to follow-up.

The study population was composed of 64 men and 39 women, with a mean age of 59.2 years (range, 24 to 80 years). Associated risk factors (Table 1) are typical of other series.[4,5] Cardiovascular surgical history was positive in 27%.

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TABLE 1. *Patient Profiles*

	AAO	CAO	GO
ASHD	35%	20%	21%
HTN	38%	48%	37%
MI	46%	17%	21%
COPD	15%	11%	11%
DM	19%	6%	16%
CVA	23%	8%	5%
Cigarette abuse	60%	62%	58%

AAO, acute aortic occlusion; CAO, chronic aortic occlusion; GO, graft occlusion; ASHD, atherosclerotic heart disease; HTN, hypertension; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CVA, cerebrovascular accident.

Statistical Analysis. Chi square analysis using a two-tail Fisher's exact test and actuarial survival curves were calculated for each presentation scenario.[6,7]

Presentation and Management

Three distinct categories of JRA occlusion emerged on analysis: group I were patients with AAO; group II, CAO; and group III were those patients with aortic graft occlusion (GO). Group I had a statistically significant perioperative mortality rate when compared with the less acute conditions found in groups II ($p = 0.009$) and III ($p = 0.015$). Group I had an actuarial survival different from groups II ($p < 0.0006$) and III ($p < 0.015$). Groups II and III were statisfically similar. Because each group had a different clinical presentation, behavior, and management strategy, they demand separate attention for this discussion.

Group I

Acute aortic occlusion was documented in 26 patients, 13 secondary to acute saddle embolus (ASE), and 13 due to thrombosis. Distribution was equally divided, with 13 men and 13 women, having a mean age of 66 years. Myocardial infarction (MI) was the primary risk factor (46%) (Table 1). Premorbid cardiac dysrhythmia was documented in 58%, requiring cardioversion in three patients.

Ischemic rest pain was the salient clinical feature (92%), whereas 35% had sensory/motor dysfunction. Because of the acute nature of the process, many patients were critically, and ultimately, fatally ill. Of particular interest, four patients (15%) presented with evidence of multiple peripheral emboli, including acute renal failure in three (mortality rate, 75%), and three patients (12%) had AAO after acute MI without death.

Operative management for AAO was determined by cause. Bilateral transfemoral embolectomy (TFE) was performed in 10 of the 13 patients (82%) with ASE; however, six required further revascularization to preserve distal perfusion. Of the remaining three patients, two had aortofemoral bypass (AF) and one had axillo-femoral bypass (AxF). In contrast, TFE was attempted four times in 13 patients with thrombotic AAO, but was successful in only one patient with abdominal aortic aneurysm thrombosis secondary to blunt trauma. Eight patients required direct aortic reconstruction by AF (62%), whereas four (31%) had AxF.

Group II

Sixty-five patients presented with 66 CAO, 42 men and 23 women, with a mean age of 57 years. The medical profile is shown in Table 1. Fifteen patients (23%) had undergone previous cardiovascular surgery.

The site of occlusion was documented by arteriography in all patients. Juxtarenal aorta occlusion occurred in 34 patients (52%), aortic bifurcation occlusion in 22 patients (33%), and occlusion of the suprarenal aorta in 10 (15%). Pathology was primarily atherosclerosis (95%); however, aortic coarctation, Takayasu's arteritis, and Buerger's disease each occurred in one patient. Disabling claudication was the primary clinical feature (92%), followed by rest pain (13%), ischemic ulceration (6%), and impotence (30% of men). No patient presented with acute symptoms.

Direct aortic revascularization was the operative management of choice. Aortofemoral bypass was performed in 56 patients (85%), with 30 of these requiring proximal aortic thromboendarterectomy (TEA). Four patients, early in the series, had aorto-iliac TEA, and one reoccluded 10 years after operation, requiring AF bypass. Visceral revascularization was a component of 25% of the aortic reconstructions (10 renal, four mesenteric).

Group III

Aortic GO occurred 21 times in 19 patients. There were 13 men and six women, with a mean age of 54 years. Comorbid conditions are listed in Table 1. Seven patients had previous cardiovascular surgery (37%). Symptoms of acute ischemia were present in 92%, whereas 8% had disabling claudication. Primary operations included one abdominal aortic aneurysm tube graft and 18 bifurcated grafts for occlusive disease. Graft size ranged from 12 to 19 mm, most commonly 14 mm (53%). Two grafts were on-lay anastomoses.

Operative management for GO included AxF (48%), redo AF (43%), and graft thrombectomy (9%). Concomitant profundaplasty was necessary in 20% to improve pelvic and distal perfusion.

Results

Group I

Eight patients with AAO had significant morbidity (Table 2), most often multisystem organ failure, which

TABLE 2. *Morbidity*

AAO	No.	CAO	No.	GO	No.
MOF	3	Mesenteric ischemia	2	MOF	1
MI	1	Pulmonary	2	Pulmonary	1
ARF	1	MOF	1	Mesenteric ischemia	1
Repeat EMB	1	Pancreatitis	1	Ureteral injury	1
		Splenectomy	1	DVT	1
		SBO	1		

AAO, acute aortic occlusion; CAO, chronic aortic occlusion; GO, graft occlusion; MOF, multisystem organ failure; MI, myocardial infarction; ARF, acute renal failure; EMB, embolism 2; DVT, deep venous thrombosis; SBO, small bowel obstruction.

occurred in three patients (12%). Perioperative mortality rate (Table 3) was 31%, and was greater for ASE (39%) than for aortic thrombosis (23%). There was one early GO requiring AxF thrombectomy and distal revascularization to improve run-off.

Follow-up demonstrates a 50% mortality rate at 1 year. Only 20% of the original cohort were alive at 10 years (Fig. 1). The cause of late death was most commonly cancer (n = 3) and cardiovascular disease (n = 3), followed by complications of diabetes (n = 1) and hip fracture (n = 1). Although survival rates are disconcerting, with a 31% perioperative mortality rate and only 20% alive at 10 years, this finding speaks to the complicated and devastating problem of AAO and the profoundly positive cardiac history. Two late graft limb failures were documented, and one AF thrombosis, necessitating AxF reconstruction.

Group II

Eight complications occurred in 14 patients with CAO (Table 2), most commonly groin lymphocele (n = 6), groin infection (n = 3), and mesenteric ischemia (n = 2). Six patients died, resulting in a perioperative mortality rate of 9% (Table 3). There were three early graft thromboses, one an aortic GO, one AF limb occlusion, and one bilateral renal artery bypass.

Follow-up showed 91% of patients alive at 1 year, 68% at 5 years, and 51% survival at 10 years (Fig. 1). The longest CAO survival was 24 years. Fourteen deaths occurred during the follow-up period, 11 secondary to MI and one each due to stroke, cancer, and multisystem organ failure. One patient developed a graft-enteric fistula 11 years after AF bypass, requiring AxF revascularization. There were three late graft limb occlusions, whereas six GO occurred during the follow-up period (0.2 to 8 years postoperatively), and are also included in the group III analysis. In addition, one patient occluded an AxF bypass and another occluded a celiac bypass.

TABLE 3. *Perioperative Mortality Rate*

	AAO (n = 8)	CAO (n = 6)	GO (n = 1)
MOF	3	1	1
Cardiac	4	1	—
Mesenteric ischemia	—	2	—
Pulmonary embolus	—	1	—
Unknown	1	1	—
Mortality rate	31%	9%	4.7%

AAO, acute aortic occlusion; CAO, chronic aortic occlusion; GO, graft occlusion; MOF, multisystem organ failure.

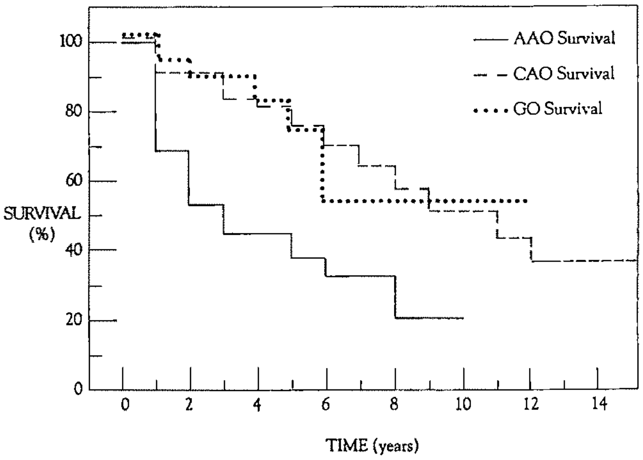

FIG. 1. Actuarial survival.

Group III

Morbidity rate for aortic GO is demonstrated in Table 2, including four amputations. One patient had an unrecognized ureteral injury during a third AF, which resulted in a urinoma. Nephrectomy was necessary because the ureter was not amenable to repair.

There was one perioperative death in a patient who presented with GO complicated by a strangulated small bowel obstruction and peritonitis. Management necessitated AxF reconstruction with lysis of adhesions and bowel resection. Multisystem organ failure led to his death 60 days after operation.

Long-term survival was 90% at 1 year, and 55% at both 5 and 10 years (Fig. 1). There were four deaths in the follow-up period, three from MI, one from stroke. Late graft thrombosis occurred in three patients, two graft limb occlusions, and one recurrent aortic GO.

Discussion

Acute Aortic Occlusion

Acute aortic occlusion is a catastrophic event. It occurs in patients with severe cardiac disease and sets in motion a series of physiologic insults that continues to have a high mortality.

Acute aortic occlusion is most commonly caused by ASE, which originates from a cardiac source. Today cardiac dysrhythmias and previous MIs are frequently encountered, whereas historically rheumatic valvular disease was a source of ASE. Additional causes of AAO include trauma, hypercoagulable states, dissection, and mycotic embolism. Thrombosis superimposed on occlusive disease is a common cause of AAO and may be difficult to distinguish from ASE. Diagnosis of AAO is straightforward. The universal symptom is acute pain accompanied by varying degrees of the classic six Ps, that is, pain, pallor, pulselessness, paresthesia, paresis, and poikilothermy. The degree of ischemia is dependent on the site of occlusion, proximal thrombosis, distal embolization, and collateral circulation.

The distinction between ASE and acute thrombosis may be difficult and relies on such historical data as previous claudication, previous embolism, cardiac dysrhythmias, recent MI, low flow state, and evidence of multiple peripheral emboli. Angiography is not mandatory but is beneficial in situations of suspected renal or mesenteric embolism.

Historically, von Bauer[8] is credited with performing the first successful aortic embolectomy in 1913. Ravdin and Wood,[9] in 1941, first reported removal of an ASE by the femoral approach. Albright and Leonard,[10] in 1950, reviewed 193 cases of ASE, finding just 34 survivors. Eight patients were cured by nonoperative means, including anticoagulation, vasodilators, intermittent venous occlusion, lower extremity cooling to reduce metabolism, and Buerger's exercises. The remaining 26 survivors were managed by direct aortic embolectomy, aortectomy, and retrograde milking of emboli from the femoral artery. The overall mortality rate in this series was 75%, whereas the nonoperative mortality rate was 95%.

In 1958, Dale and Mahoney[11] reviewed 64 successful aortic embolectomies and concluded that immediate operation was the treatment of choice. Willman and Hanlon[12] (1959) reported four successful saddle embolectomies through the femoral artery under local anesthesia without death. In 1962, Deterling et al.[13] reported 22 cases of ASE with an operative mortality rate of 66%.

The operative management of arterial embolism was forever changed by the introduction of the balloon-tipped embolectomy catheter by Fogarty et al (1963).[14] Porter et al.,[15] in 1966, reported a series including 16 "conventional embolectomies" compared with six catheter embolectomies. The catheter technique reduced operative time by 50% and transfusion requirements by 75%. More importantly, operative mortality rate dropped from 50% to 33%, and limb salvage rose from 44% to 100%. Recent reports[4,16] confirm the enhanced survival and limb salvage rates associated with balloon catheter TFE.

Acute aortic thrombosis was described by Bell[17] (1967) as a terminal event associated with severe iliofemoral occlusive disease and progressive cardiac failure. He recognized the futility of thrombectomy and advocated bypass of the thrombosed segment from the infrarenal aorta to the femoral arteries. Despite these observations, his mortality rate was 100%. Danto et al.,[18] in 1972, however, treated eight patients with AAO using aortoiliac or AF bypass. Mortality rate was 25%, although the morbidity rate remained high.

Thrombosis of abdominal aortic aneurysm was first reported in 1959 by Shumacker,[19] but Janetta and Roberts (1961)[20] are usually credited. The largest series is by Johnson et al.,[21] who, in 1974, reviewed 15 cases with an operative mortality rate of 53%.

This series of 26 AAOs, having a limb salvage rate of 98% and mortality rate of 31%, compares with other large series. On diagnosis, systemic anticoagulation is begun with intravenous heparin sodium to inhibit proximal and distal thrombosis. Often patients are profoundly decompensated, displaying both local and systemic effects of ischemia, including variable degrees of cardiac failure with intravascular volume depletion, acidemia, and hyperkalemia. They also may have acute renal failure or mesenteric ischemia.

Aortography is not mandatory unless renal or mesenteric involvement is suspected, although it was performed in 50% of this series. Operation is imperative for survival. In our experience, TFE had a disappointingly low success rate as the sole means of revascularization. Even with ASE, TFE was enhanced with a bypass procedure in 60% of cases. Nonetheless, TFE using local anesthesia is, theoretically, the safest and most expeditious means to revascularize these critically ill patients. If TFE only clears one iliofemoral system, a femoral–femoral crossover should be used. If adequate inflow is impossible bilaterally, a judgment must be made regarding the potential for successful aortic reconstruction. Most circumstances dictate extra-anatomic bypass grafting through AxF, and the patient should be prepared for such a contingency at the outset.

Anticoagulation is continued after operation. Patients must be evaluated for evidence of compartment syndrome, acid washout from reperfused muscle and gut, myoglobinuria, and recurrent embolization. Cardiac complications and multisystem organ failure are the most frequent causes of death.

Long-term anticoagulation with warfarin has been shown to prevent re-embolization.[4] Patients in this series were not routinely managed with warfarin until 1982. One patient, however, required amputation while still hospitalized after reembolization while being treated with heparin.

Acute aortic occlusion continues to present life-threatening surgical challenges. Rapid diagnosis, resuscitation, and revascularization must occur, cognizant of the physiologic milieu of acute ischemia, to achieve survival. Despite advances in critical care medicine and surgical techniques, mortality rate remains high.

Chronic Aortic Occlusion

The clinical presentation, management, and outcome of CAO contrasts that of AAO. Chronic occlusive disease of the terminal aorta has been recognized to cause claudication and impotence at least since LeRiche[1] described the syndrome in 1923; however, CAO is rare, noted only in 0.15% of 33,216 autopsies.[22]

Manifestations of CAO include bilateral lower extremity claudication and absent femoral pulses. There is a predilection toward males with a strong history of tobacco abuse. Other features include ischemic rest pain and impotence. Acute ischemia is not a clinical finding because of the progressive nature of the disease and the opportunity for the development of collateral circulation. As such, these patients do not have the physiologic insult found in AAO and may be evaluated and managed electively.

In 1963, Bergan and Trippell[23] recognized JRA occlusion as a terminal stage of LeRiche syndrome because of continued proximal thrombosis. They described JRA endarterectomy with distal revascularization by bypass graft or TEA. They advised renal cross-clamping before aortic manipulation to avoid embolization and, further, advocated hypothermia and mannitol infusion for renal protection from ischemic injury. Chavez et al.,[24] in 1968, reported three cases of successful proximal aortic TEA for juxtarenal CAO using temporary occlusion of the renal arteries without hypothermia.

Starrett and Stoney[22] (1974) reviewed a large experience with JRA occlusion receiving either medical or surgical management. The nonoperative group had documented proximal propagation of thrombosis into the renal and mesenteric circulation with ensuing visceral ischemia. In the operative group (n = 40), 17 extensive aortic TEAs demonstrated the primary occlusive lesion to be distal to the inferior mesenteric artery or in the origin of the common iliac arteries. They noted that occlusion proximal to the primary lesion was due to thrombosis, often in the absence of significant aortic intimal hyperplasia. Follow-up disclosed an 85% patency at 10 years; however, 10-year survival was only 37%.

Several published accounts appeared in the early 1970s describing remote bypass procedures designed to treat proximal aortic occlusive disease. Nunn and Kamal,[25] in 1972, first reported a descending thoracic to femoral artery bypass using a retroperitoneal approach. The authors recommended that this procedure only be considered in low-risk patients. In 1974, Frantz et al.[26] described an ascending aorta to femoral artery bypass for a singular patient in whom the abdominal aorta was found to be unsuitable for grafting. This approach requires a median sternotomy and, as such, has not been widely used. Such remote bypass procedures, including AxF, have been condemned for the management of CAO because they do not eliminate the risk of proximal thrombosis. In one report, extension of thrombosis to the level of the renal or mesenteric arteries accounted for a 46% mortality rate in untreated patients, compared with a 10% operative mortality rate.[22]

Liddicoat et al.[27] (1975) reported standardized operative techniques for proximal aortic TEA and onlay AI or AF bypass. Perioperative mortality rate was 4.6%, with a low morbidity rate and favorable long-term results in 64 patients.

A fundamental debate concerned the need for in-line aortic reconstruction to remove the thrombus and prevent proximal propagation. Although Starrett and Stoney[22] demonstrated devastating complications and death from proximal thrombosis, others found the antithesis true. In one group of patients with CAO treated medically or with AxF, none of the 13 patients available for follow-up demonstrated proximal thrombosis of visceral vessels.[28]

The debate continued regarding the risk of proximal thrombosis, as Deriu and Ballotta[29] (1983) demonstrated arteriographic and pathologic evidence for progressive ascending thrombosis of the occluded aorta. This controversy is not likely to be settled without a prospective, randomized trial to include nonoperative therapy, direct aortic reconstruction, and extra-anatomic bypass. Follow-up would involve serial arteriography to document the nature of disease progression. Because a study of this nature is unlikely to be performed, it is prudent to acknowledge the potential for clot propagation and consequential acute renal failure or mesenteric ischemia, and recommend direct in-line aortic reconstruction.

Aortic Graft Occlusion

There exists a large body of literature discussing aortic graft limb occlusion, but there is little concerning complete occlusion of an aortic graft. Robiscek et al.[30] (1985) dispelled an early myth that woven and knitted grafts had dissimilar failure rates, concluding that graft thrombosis is rare and is usually related to poor technique, disease progression, and chronic cigarette abuse.[31] Naylor et al.[32] reported 46 GOs in 28 of 241 patients evaluated after AF. There were five bilateral occlusions, not otherwise distinguished from the single limb occlusions. Others confirm these observations in longitudinal studies of AF efficacy.[33,34]

We believe this experience of 21 aortic GOs is the largest yet presented. Five grafts were implanted at another institution, leaving 16 implanted by this practice. During the study period, a total of 4126 aortic graft procedures were performed, 1073 tube grafts and 3053 bifurcation grafts. The thrombosis rate for tube grafts (n = 1) is 0.09%, compared with 0.5% for bifurcated grafts (n = 15). Two onlay grafts occluded and were replaced by in-line grafts.

The importance of the profunda femoris artery in maintaining graft patency has been emphasized previously,[35] and profundaplasty accompanied five of nine redo AFs. Graft occlusion occurred early (median, 1.3 years) but, once corrected, reasonable survival and limb salvage can be expected.

Patients with aortic GO represent a hybrid group that manifest features of acute ischemia, albeit less severe than AAO. This insult is tolerated well, with a lower perioperative mortality rate and good long-term survival. Most patients had original reconstructive procedures for occlusive disease; hence there was already well-developed collaterals to maintain limited perfusion to the pelvis and lower extremities.

Seven of 21 GOs occurred after previous aortic occlusions (six CAO, one AAO). Presentation did not include the poor cardiac function and end-organ ischemia found in AAO. Preoperative management included early anticoagulation with heparin sodium, arteriography, and expeditious revascularization. Bilateral TFE was performed in two patients, though it proved to be a temporizing measure because both patients subsequently returned with another aortic GO.

Aortic GO must be viewed as a technical failure secondary to redundant graft, a distal anastomotic problem, or the result of progressive outflow occlusive disease. Simple graft thrombectomy will not correct the underlying problem. Revascularization requires redo AF or extra-anatomic bypass. In either case, attention to the profunda femoris artery is important in providing run-off for proximal graft patency, because many patients have concomitant superficial femoral artery occlusion. The long-term patency of redo aortic grafts should approach that of primary aortic reconstructions and, thus, afford an improved functional result when compared with AxF.

Conclusion

In summary, JRA occlusion can be viewed as a spectrum of disorders ranging from AAO in a profoundly ill patient, through acute lower extremity ischemia found in GO, to chronic vascular insufficiency in CAO. The presentation, management, and expected outcome vary by cause. Despite advances in critical care medicine and specialized vascular and anesthetic techniques, AAO still has a poor prognosis. The principles of current therapy include rapid diagnosis, operative management, and anticoagulation. The future holds improved survival as we learn to pharmacologically manipulate ischemic physiology and preserve end-organ function.

In contrast, patients with acute GO and CAO survive their insults reasonably well. In-line aortic reconstruction for CAO results in durable limb preservation with improved function. Graft occlusion should continue to be managed with anticoagulation and expeditious revascularization. Attention must be directed, however, to the identification and correction of the underlying cause of graft failure. Long-term limb salvage and preservation of function can be achieved with diligence.

Acknowledgment

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DISCUSSION

DR. LARRY H. HOLLIER (New Orleans, Louisiana): I appreciate Dr. Edwards sending me a copy of this paper. I am glad he did in advance because it has so much information in it. It really is a massive work, Bill, and I think you are to be congratulated; and your colleagues who did a lot of the background work in reviewing this information are certainly to be congratulated. It represents one of the most extensive experiences and is very well documented. I have several questions about this. How many were lost to follow-up over that period, and would it make any difference in your survival rates? Secondly, in the acute occlusion patients, you have noted throughout the study fair morbidity and mortality rates. Although they seem to be high, they are actually what is expected and are almost the same mortality and morbidity rates that we have seen in our own patients with acute problems. These patients are sick, and multi-organ problems do occur. In view of the high mortality rate despite early and aggressive therapy, what are your thoughts concerning any role that there might be for lytic therapy in these patients? Do you think that that would make a difference? About 10 or so years ago, Jack Wiley, Stoney, and Ehrenfeld commented about the risk of renal artery occlusion in patients with complete aortic obstruction. You noted in your presentation and in the paper that no patient presented with renal failure. But did you see evidence that would confirm Wiley's expectation that these would progress up and occlude? And, finally, in the graft occlusion group, it is my own experience that end-to-side anastomoses in the aorta would appear to have a higher rate of graft failure from hemodynamic disturbances and neointimal fibroplasia. Could you tell any difference in these patients? Were these primarily end-to-end, end-to-side, or were they mixed? Thank you.

DR. STANLEY O. SNYDER, JR. (Norfolk, Virginia): Dr. Edwards, I enjoyed your presentation and the opportunity to review this large manuscript also. As Larry said, the magnitude of this series is impressive and is "Houstonoid." I think the results are truly commendable, and I would like to comment on a couple of points and ask several questions. The mortality rate for acute aortic occlusions was actually quite good at 31%, despite the increased requirements perhaps surgically for aortofemoral reconstruction in two thirds of the thrombotic occlusions and in two of three of the unsuccessful embolectomy patients. I think the increased operative risk in the elective chronic aortic occlusion is highlighted by your 9% mortality rate, compared with only a 2.6% mortality rate in the remaining 4100 patients in this series. The adjunctive 10 renal and four mesenteric revascularizations attest to the severity of disease and may have contributed to the increased mortality rate in this group. A somewhat disturbing finding in the chronic occlusive group was postoperative graft occlusion in six of the 66 patients, compared with only eight occlusions in the remaining 4100 patients in the series. My questions are, do you have a standard preoperative cardiac or medical evaluation to help to determine whether aortic reconstruction *versus* axillofemoral bypass might be best? Secondly, do all patients with chronic aortic occlusion require elective reconstruction? And, if not, in light of Dr. Stoney's and Dr. Hollier's comments today, do you think that these patients should be on chronic anticoagulation?

The other question concerns whether you know what the cause of graft occlusion was? You only had to do a profundaplasty in 20% of the patients who had aortic graft failure. I wondered about the possible cause for the other 80%. And, lastly, as with Larry, I would like to know if you think there is a role for thrombolytic therapy in these patients who are not in jeopardy for limb loss. Thank you.

DR. WILEY F. BARKER (Los Angeles, California): Mr. President, Members and Guests, I want to compliment Dr. Edwards and his group on this presentation. And I have three slides that I would offer that I hope will be complementary to this. The first slide shows an acute occlusion of the kind that he is talking about. Well, it was not that acute; the patient was a very big and husky oil field worker with about 5 weeks of acute, occlusive symptoms and ischemia, and we were astonished to find a 5- or 6-cm aneurysm in this man. There is nothing further to say about him, except that a few weeks later we saw a patient whom I can show better in this artist's drawing. There was a slight infundibulum showing below the renal artery, and we thought we had a classical infrarenal occlusion. When we entered the abdomen, that little infundibulum just tapered off into some fibrous bands that trickled down and finally joined what turned out to be a reconstitution of the iliac arteries with the extensive collateral. These are two quite different patterns of juxtarenal occlusion. I would point out that this man was in his 50s and had had no evidence of renal disease, perhaps a comment on the questions that were raised about the risk of renal involvement. The third slide then is probably the oldest slide shown in any of these meetings recently; this is a sketch from an 1835 paper by a man named Barth, who described the first patient, as far as I am aware, in which clinical claudication was clearly manifest. The patient happened to die of natural heart disease rather than of this, but was severely handicapped. If this is an acute and proper representation, this either represents a chronic and neglected aortic occlusion or a form of the hypoplasia that I showed in the second slide. I thought this might be of some interest because it probably even antedates the Houstonian work in this area. I want to compliment you again, and thank you for the privilege of discussing it.

DR. CARLOS M. CHAVEZ (Brownsville, Texas): Dr. Ochsner, Dr. Jones, I think this is another well-structured and well-presented paper by Dr. Edwards' group. It contains a lot of information. I have not had a chance to review the paper, but I am going to limit my comments to those cases of juxta-aortic occlusion.

Nearly 20 years ago, we described various techniques of treatment of what we labeled at that time high aortic or high Leriche's syndrome, that is, juxtarenal occlusion. Our results with 25 patients has been excellent in the short- and long-term follow-up. Our choice of treatment or anastomoses for the proximal part has been the end-to-end anastomoses, and temporary occlusion of the renal arteries at the time of the reconstruction has been essential. I would like to ask Dr. Edwards if he has or encountered any problems, renal problems, at the time of the reconstruction and how he handled the renal arteries at the time of thrombectomy that is done before the anastomoses.

DR. S. SCOTT TAPPER (Closing discussion): I would like to begin by thanking each discussant for their kind and valuable remarks. Dr. Hollier, our follow-up in this series was 100%. With the diligence of Dr. Edwards and his nurse Judy Jenkins, we were able to track down every single patient in this series. Our acute aortic occlusion did have an operative mortality rate of 31%, which is within the range of other published series. You asked if we had considered using lytic therapy. In fact this modality has not been used by us. Other people have reported the use of lytic therapy as an adjunct to reopening an occluded graft, but as you know, all of these reports are fraught with a high incidence of complication, and nearly every patient that had a graft reopened subsequently underwent an operative procedure anyway. With regard to chronic aortic occlusion and renal artery occlusion, we were not able to document and follow any patient that subsequently progressed to renal artery occlusion from a chronically occluded aorta. In our series of graft occlusions, we did have two grafts that were end-to-side on-lay aortic bifurcation grafts. The rest were in-line, end-to-end anastomoses.

Dr. Snyder, our preoperative assessment did not contain any formal elements other than a careful history and physical examination, and any further workup that was required was brought out from that history and physical examination. You asked an interesting question: Do all chronically occluded aortas require revascularization? We do not know the answer to that. In our series, we did revascularize every chronically occluded aorta that we encountered. There have been other series in which patients with a chronically occluded aorta were not revascularized, and these patients showed a progression of disease with the involvement of the renal and mesenteric arteries. The cause of the graft occlusion can be uncovered in the operating room. And although profundaplasty was not always performed, we did have occasion to resect some false femoral aneurysms; we did notice some kinks in grafts; and there were some proximal anastomotic problems that accounted for some of the graft occlusions.

Dr. Barker, thank you for your kind remarks. I noted during my research for this paper that you presented a very significant series of acute saddle embolus to this organization about 9 years ago. It was interesting to note that Dr. Dale discussed that paper.

Dr. Chavez, we did not encounter any specific problems with renal arteries during the operations. Our standard treatment is to dissect them out, but we do not clamp the renal arteries before cross-clamping the aorta.

I would end by thanking Dr. Edwards and the Association for the privilege of discussing this paper.

Current Management of Male Breast Cancer

A Review of 104 Cases

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Between 1975 and 1990, 104 male patients with a total of 106 breast cancers were treated at Memorial Hospital or the Ochsner Clinic and their records reviewed. The patients were followed for a median of 67 months (range, 0.5 to 14.4 years). Analysis of the frequency distribution by stage showed that 16 (17%) patients were stage 0 and 26 (27%) patients were stage I. The median duration of symptoms before diagnosis was 18 weeks (mean, 5 weeks; range, 1 to 156 weeks). Modified radical mastectomy was undertaken in 71 (67%) patients. The actuarial 5-year relapse-free survival for the entire group was 68% and the actuarial 5-year overall survival was 85%. Relapse-free survival at 5 years for axillary node-negative patients was 87% and for node-positive patients was 30% ($p < 0.001$). Overall survival figures for the same subsets showed a 5-year survival of 100% for the node-negative subset and 60% for the node-positive subset. On multivariate analysis, the most powerful predictor of outcome in men was the status of the axillary lymph nodes, and the only prognostic factor that added significantly to this predictive power was the duration of symptoms. Patients who sought treatment less than 6 months after the onset of symptoms experienced a significant survival advantage when compared with patients whose symptoms were present for more than 6 months ($p = 0.03$). The profile of the stages at diagnosis, the treatment approach, and the survival rates approximate those reported in series of female breast cancers, and overall, the two diseases are remarkably similar.

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ALTHOUGH BREAST CANCER in men is an uncommon disease, occurring less than 1% as often as in women, in 1991 an estimated 900 men in the United States will be diagnosed as having invasive breast cancer, and 300 of these will be expected to die of the disease.[1] Breast cancer represents less than 1% of all malignancies in males. Because of its rarity, carcinoma of the male breast has not been studied as extensively as carcinoma of the female breast, and this fact has prompted us to combine the experience of two institutions in a retrospective analysis.

Materials and Methods

From 1975 to 1990, 104 men with 106 primary operable breast carcinomas (two were synchronously bilateral) were treated at either Memorial Hospital or the Ochsner Clinic. Patients with clinical evidence of distant metastases or supraclavicular lymph node involvement at the time of presentation have been excluded.

Follow-up was obtained by direct contact with the patient or his family. The cause of death of patients was obtained from autopsy reports and death certificates, when available, or by correspondence with the hospital and physician caring for the patient at the time of his death.

The TNM (tumor, nodes, and metastasis) staging was based on the pathologic size of the tumor and the pathologic extent of axillary node metastases.

Univariate statistical analyses of each prognostic factor was carried out using the Kaplan–Meier product limit method[2] and the log-rank test. The Cox regression method[3] was used in the multivariate survival analyses to identify a combination of factors that significantly impacted on survival. Wherever feasible, hazard plots were performed to assess the appropriateness of the proportional hazards assumption that underlies the Cox regression model. Log-likelihood ratio tests were used in the multivariate analysis to assess the significance of factor combinations.

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Results

The median age at diagnosis of the men in this series was 58 years of age (mean, 61 years; range, 25 to 83 years). The median length of follow-up was 67 months (mean, 68 months; range, 6 months to 15 years).

Specific details concerning the time interval between the onset of breast symptoms and the definitive surgical management of the breast cancer (duration of symptoms) were available on 93 patients. The median duration of symptoms was 18 weeks (mean, 5 weeks; range, 1 to 156 weeks). The presenting symptom was a mass in 77 (74%) patients. Bloody nipple discharge was present in 16 (15%) patients, and nipple retraction was the presenting symptom in 18 (17%) patients. Most patients had more than one symptom.

Preoperative mammography was obtained in 50 patients. Twenty-nine (58%) patients had an identifiable mass on mammography. Four (8%) patients had microcalcifications alone, and 13 (26%) patients had an architectural deformity. Mammography was falsely negative in four (8%) patients.

Clinically significant gynecomastia was present in 24 (23%) patients. None of the patients in this series had a history of Klinefelter's syndrome, none had a history of feminization, none had undergone orchiectomy, and none were sterile. Twelve (11.5%) patients gave a history of trauma to the involved breast within 2 years of the diagnosis of breast cancer.

Details concerning family history of breast cancer were available in 87 patients. Twelve (14%) patients had a first-degree relative with a history of breast cancer. Eight (9%) patients had a history of a second-degree relative with breast cancer. Four patients had two first-degree relatives with breast cancer, three patients had three first-degree relatives with breast cancer, and one patient had four first-degree relatives (all sisters) with breast cancer.

In 29 patients (27%), the tumor was centrally located, the most common site of the primary lesion. The second most common location was the 12 o'clock axis. Five patients presented with clinical inflammatory carcinoma that was confirmed pathologically. Skin ulceration was a component of the disease in 10 patients at presentation, and three patients presented with tumors that were fixed to the pectoralis major muscle. Seven patients presented with Paget's disease of the nipple.

TABLE 1. *Type of Surgery*

Type of Mastectomy	No. (%)
Modified radical	71 (67)
Radical	28 (26)
Total	5 (5)
Extended radical	1 (1)
Wide excision	1 (1)
Total	106 (100)

* Total of 104 patients. Two patients had synchronous bilateral disease, and both underwent bilateral modified radical mastectomy.

TABLE 2. *Histologic Types of Male Breast Cancer*

Histologic Type	No. of Patients (%)
Ductal carcinoma *in situ*	16 (15)
Infiltrating duct	36 (34)
Infiltrating duct + ductal carcinoma *in situ*	51 (48)
Medullary/tubular	2 (2)
Unspecified	1 (1)

The diagnosis of carcinoma of the breast was made by open biopsy in 91 (87.5%) patients and by cytologic examination of fine needle aspirate specimens alone in eight (8%) patients. The type of biopsy was not specified in seven cases.

The most common surgical procedure employed in the management of these carcinomas was modified radical mastectomy (71 patients, 67%). Radical mastectomy was employed in 28 (26%) patients, total mastectomy in 5 (5%) patients, extended radical mastectomy in 1 patient, and wide excision alone in 1 patient (Table 1).

The most common histologic type of breast cancer in men was the combination of infiltrating duct carcinoma with a component of duct carcinoma *in situ* (51 patients, 48%). Ductal carcinoma *in situ* alone was the diagnosis is 16 (15%) patients (Table 2). Lobular carcinoma was not seen. Lymphatic invasion was present in 18 of 77 (23%) patients. Similarly, details concerning multicentric foci of carcinoma in the index breast were available on 75 patients, and seven (9%) of these were positive. The stage at presentation was as follows: stage 0, 16 (17%) patients; stage I, 26 (27%) patients; stage II, 32 (33%) patients; stage III, 21 (22%) patients.

The status of the axillary lymph nodes was known in 99 patients. Thirty-seven patients (38%) had pathologically positive nodes at the time of diagnosis. A full three-level axillary dissection was performed in 60 patients. The average number of axillary nodes removed was 20. Negative level I nodes with involved level II nodes (skip metastases) were seen in four (4%) patients. Nine (15%) patients had involved level III axillary nodes. One patient had positive Rotter's nodes.

Details concerning the status of the steroid hormone receptors were available in a subset of patients. The status of the estrogen receptor protein was available in 46 patients, 38 (83%) of whom were positive. The status of the progesterone receptor protein was available in 42 patients, and 32 (76%) were positive.

Details concerning adjuvant therapy were available in 92 patients. Thirteen patients received cytotoxic chemotherapy, and seven patients received tamoxifen. Adjuvant radiation therapy was administered to three patients, and adjuvant endocrine ablative surgery by orchiectomy in three patients.

TABLE 3. *Status at Last Follow-up*

Status	No. of Patients (%)
No evidence of disease	61 (58)
ASU	3 (3)
Alive with disease	5 (5)
DOC	13 (12)
Dead of disease	22 (21)

ASU, alive, status unknown; DOC, dead of other causes.

The status at last follow-up for this patient population is summarized in Table 3. Nineteen patients (18%) suffered a distant relapse. The most common site of distant relapse was the bone, occurring in 15 patients (83%). The second most common site of distant failure was the lung. Five patients suffered a local regional relapse (4.8%). Among the subset of 37 axillary node-positive patients, 13 patients suffered a distant relapse (35%). Subsequent contralateral breast cancers occurred in five patients.

The actuarial 5-year relapse-free survival for the entire group was 68%, and the actuarial 5-year overall survival was 85% (Figs. 1 and 2). Relapse-free survival at 5 years for axillary node-negative patients was 87% and for node-positive patients was 30% ($p < 0.001$). Overall survival figures for the same subsets disclosed a 5-year survival of 100% for the node-negative subset and 60% for the node-positive subset (Fig. 3). Analysis of overall survival by stage disclosed a 5-year survival of 100% for stage 0 patients, 83% for stage 1 patients, 70% for stage 2 patients, and 74% for stage 3 patients. The inconsistency between stage 2 and stage 3 survival resolves itself when a follow-up of 90 months is reached, at which time stage 3 patients begin to do worse than stage 2 patients.

On multivariate analysis, the most powerful predictor of outcome in men with breast cancer is the status of the axillary lymph nodes (Table 4). The only factor that added significantly to the predictive power of the node status was the duration of symptoms.

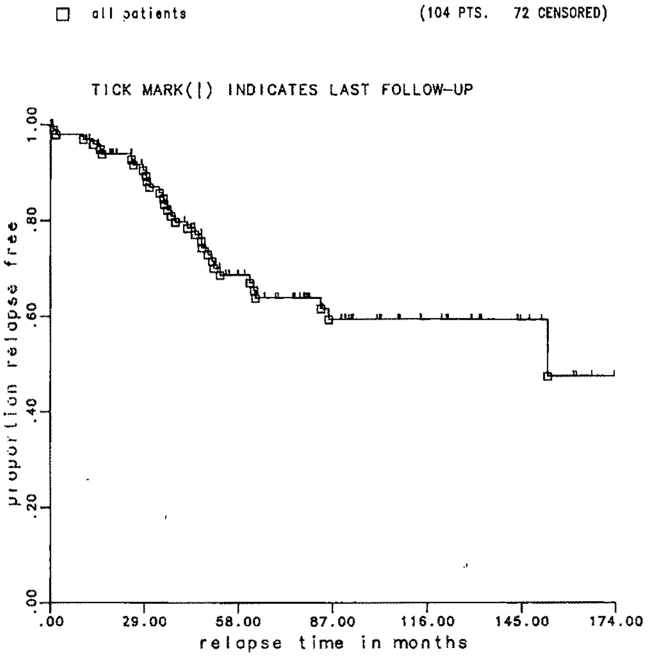

FIG. 1. Actuarial Kaplan–Meier plot of relapse-free survival after treatment of carcinoma of the male breast.

Discussion

Wainwright[4] is generally credited with the first published report of a male breast cancer, in which he proclaimed the lethality of the disease. Recognition for the first report of male breast carcinoma, however, should actually be given to the 14th century British physician, John of Arderne.[5] He discovered an enlarging mass beneath the right nipple in a priest of Colstone. A local barber-surgeon promised cure, but John "would let no cutting come there nigh."

Accurate pedigrees in male breast cancer patients have been poorly documented. In a collective series, Crichlow[6]

TABLE 4. *Predictors of Outcome in Male Patients With Breast Cancer*

Factor	p (Univariate)	p (Multivariate)
Axillary lymph nodes	<0.001	<0.001
Duration of symptoms†	0.01	0.03
Tumor size‡	0.04	NS
Age at diagnosis§	NS	NS
Estrogen receptor	NS	NS
Progesterone receptor	NS	NS

* Cox regression method.
† Population dichotomized at symptom duration of 6 months.
‡ Analyzed as a continuous variable.
§ NS, not significant. Significance defined as $p \leq 0.05$.

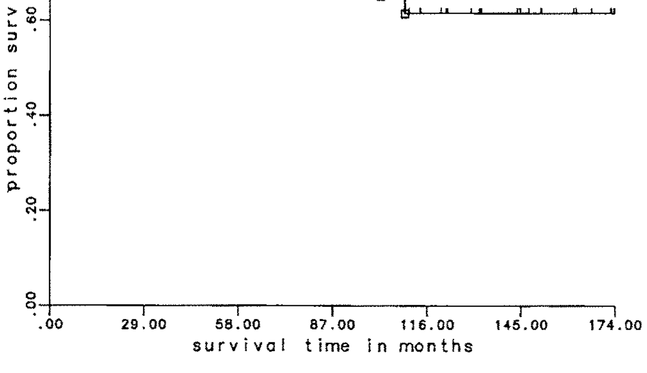

FIG. 2. Actuarial Kaplan–Meier plot of overall survival after treatment of carcinoma of the male breast.

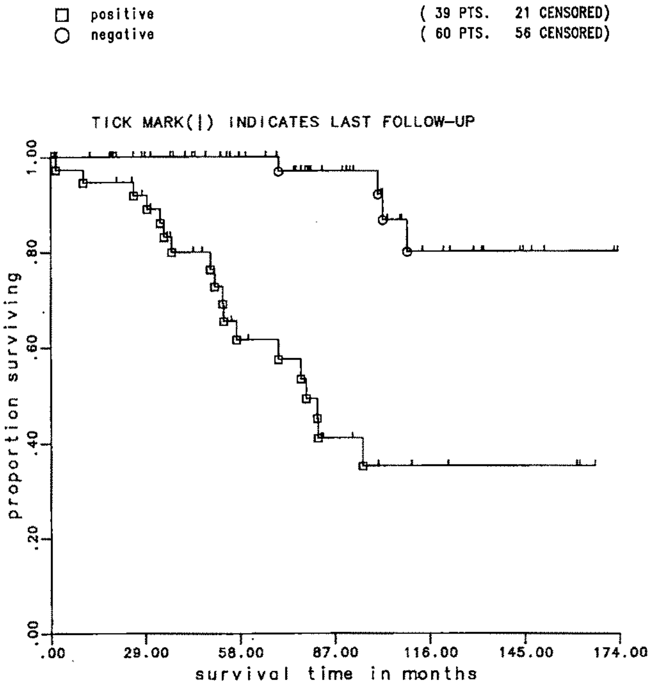

FIG. 3. Actuarial Kaplan-Meier plot of overall survival as a function of the status of the axillary lymph nodes initially.

found 10 cases of carcinoma of the breast in female blood relatives of 79 men with breast cancer. Most of these were not first-degree relatives. Rare families have been reported in which several males have developed breast cancer.[6-12] Our incidence of 14% of first-degree relatives with breast cancer is higher than other reported series.

The cause of carcinoma of the breast is no better understood in men than in women, but intrinsic differences in the target organ and hormonal milieu between the sexes provide a unique opportunity for study. Causative factors that have been implicated in the development of male breast cancer include hyperestrogenism, Klinefelter's syndrome (sex chromosomes XXY), gynecomastia, trauma, and radiation injury.[13-17] None of the patients in the current study had Klinefelter's syndrome, sterility, or exposure to ionizing radiation therapy. Twenty-four patients (23%) had clinical gynecomastia. Gynecomastia does not seem to be associated with the development of breast cancer. In Crichlow's review,[6] only 17 (3%) cases of gynecomastia were reported among 625 male breast cancer patients. The microscopic appearance of gynecomastia (*i.e.*, fibroepithelial hyperplasia and stromal hypertrophy), however, may actually be more common. In a review of male breast cancer patients treated at Memorial Hospital, whose cytologic material was reviewed by Heller et al.,[18] 40% were found to have microscopic evidence of gynecomastia.

Historically, male breast cancer patients typically present with a more advanced stage of disease than do women.[18-21] A comparison by stage of disease at presentation for four groups of breast cancer patients, the current study of men treated between 1975 and 1990, men treated between 1960 and 1975 at Memorial Hospital, and women seen in calendar year 1989 at Memorial Hospital and the Ochsner Clinic, can be found in Table 5. For stage 0, stage I, and stage II, the pattern appears to approximate the distribution seen in female breast cancers. There remains a preponderance of stage III patients in the male subset.

In earlier series before 1951, an average delay of 18 months between the onset of symptoms and the commencement of treatment was described.[6] In the later collected series of 587 cases, an average delay of 10 months occurred.[22] The median delay of 18 weeks (mean, 5 weeks) reported in this series is considerably shorter than the treatment delay reported in prior series. On multivariate Cox regression analysis, the duration of symptoms was the only prognostic factor that added consequentially to the predictive power of the axillary lymph node status. Patients with a delay in treatment of less than 6 months experienced a statistically significant overall survival benefit when compared with men whose symptoms were present for longer than 6 months (p = 0.03) (Table 4 and Fig. 4).

The median age at which male breast cancer is diagnosed is several years later than in women. In the Crichlow series, it was 59.6 years.[6] The earlier series reported by Holleb et al.[5] gave a median age of 56, but in a more recent series it was 65 years.[23] Male breast cancer has

TABLE 5. *Comparison of Stage of Disease in Groups of Men and Women*

		Stage			
Sex	Study Group	0	I	II	III
M	1975–1990	16/95 (17%)	26/95 (27%)	32/95 (33%)	21/95 (22%)
M	1960–1975*	8/77 (10%)	21/77 (27%)	37/77 (48%)	11/77 (14%)
F	Memorial Hospital, 1989†	173/932 (18%)	300/932 (32%)	365/932 (39%)	55/932 (6%)
F	Ochsner Foundation Hospital, 1989‡	25/162 (15%)	69/162 (43%)	51/162 (32%)	17/162 (10%)

* Heller K, Rosen P, Schottenfeld D, Ashikari R, Kinne D. Male breast cancer: a clinicopathologic study of 97 cases. Ann Surg 1973; 188: 60–65.

† Patients treated on the Breast Service, Memorial Hospital, New York, 1989. Forty patients were either stage IV, or women not able to be staged.

‡ Patients treated in the Department of Surgery, Ochsner Clinic, New Orleans, 1989.

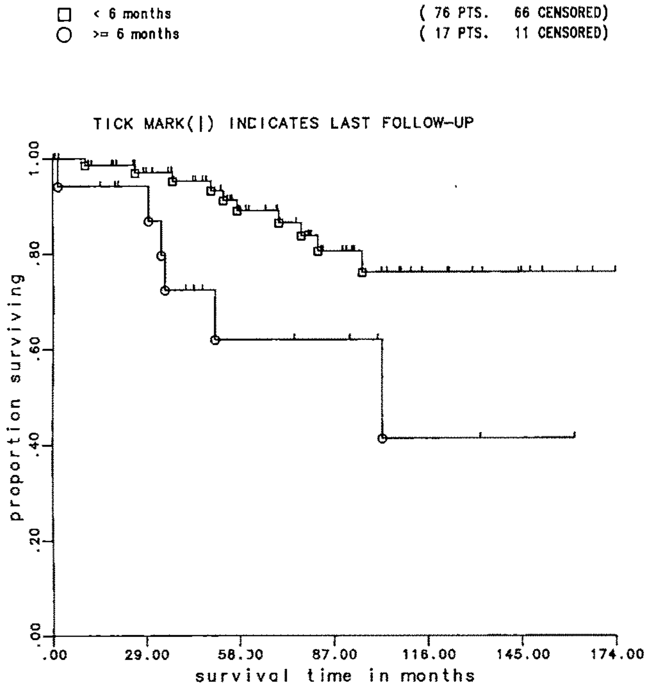

FIG. 4. Actuarial Kaplan-Meier plot of overall survival as a function of duration of symptoms. Information about duration of symptoms was available for 93 patients. The subset has been dichotomized at a symptom duration of 6 months.

been reported in patients as young as 5 years of age and as old as 93 years. The age at diagnosis of patients in our series did not impact on survival on multivariate analysis.

The reported incidence of bilateral breast cancer in men, 1.4% of 1158 patients, is lower than in women. This may be due to a poorer prognosis from the primary cancer and the later age of diagnosis, with patients dying of other causes. In our series, two patients presented with synchronous bilateral disease and an additional five patients developed metachronous contralateral breast cancers. The reasons for this high rate of bilaterality are not clear, but may be a reflection of the increased numbers of early stage patients and their improved survival.

The standard surgical approach to male breast cancer in most reported series has been radical mastectomy. In the past several years at our institution, however, the modified radical mastectomy has supplanted the radical mastectomy in most cases. The transition has primarily been the result of the fact that patients are presenting with an earlier stage of disease. It should be noted, however, that radical mastectomy has not been abandoned as a treatment option for male breast cancer and is appropriate for lesions that invade the pectoralis major muscle or lesions with involved Rotter's nodes. Two of the authors (PIB and WMPM) would prefer to treat patients with locally advanced cancer on a protocol of primary cytotoxic chemotherapy followed by toilet mastectomy and chest wall irradiation.

Recently, adjuvant systemic therapy has been advised for male patients with pathologically involved axillary lymph nodes. At our institutions, this involves combination chemotherapy similar to that given in female breast cancer patients, with antiestrogen therapy in patients who are estrogen receptor positive. Little has been written on the subject of systemic therapy in male breast cancer. These analyses are difficult to interpret because of the need to review collective series.[24,25] In our series, 13 patients received cytotoxic chemotherapy (Table 6). Six (46%) of these patients suffered a distant relapse. Fourteen patients were axillary node positive and did not receive any adjuvant therapy. In this subgroup, eight (57%) suffered a distant relapse. The small numbers involved preclude meaningful statistical analyses. A review of the literature suggests that the alkylating agents and doxorubicin are the most effective agents in the treatment of male breast cancer, although few drugs have been adequately tested.

Kinne and Hakes[26] have summarized the literature of hormone manipulations in male breast cancer. The picture is encouraging; the overall response rate to hormonal manipulation is 51%, and reaches 71% if estrogen receptor protein is positive. The authors warn that the literature in this area is sparse, however, and most reports on ablative procedures are from an earlier era when response criteria were ill defined. In our series, seven patients received tamoxifen, and one (14%) recurred systemically. None of the patients experienced any side effects to the tamoxifen.

In Crichlow's collective series and others, most results indicated that men with breast cancer had a poorer prognosis than women.[6,27–35] The 5-year survival rate was 49% overall, ranging from 79% in the node-negative group to 28% if nodes were involved. Our 5-year survival of 100% in the node-negative group may be a partial reflection of the relatively higher number of stage 0 patients in our series. In the few series in which 10-year results were given, overall survival was 35% (62% if nodes were negative and only 4.3% in the node-positive subgroup). Pathologically involved axillary lymph nodes were observed in 55% of specimens, a significantly larger proportion than the 38% reported in the current study, and is possibly a reflection of treatment delay. Other reports have suggested that

TABLE 6. *Adjuvant Treatment in Male Patients With Breast Cancer*

Adjuvant Therapy	No. of Patients	Positive Axillary Nodes No. (%)	Distant Relapse No. (%)
CMF	12	11/12 (92)	6/12 (50)
CAF	1	1 (100)	0
Tamoxifen	7	5/7 (71)	1/7 (14)

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil.

breast cancer in men carries a prognosis that is similar to the outcome in the female form of the disease.[36–44]

The series reported by Heller and colleagues[18] reported 5- and 10-year results by clinical and pathologic stage and compared these results in men with an earlier experience in women reported by Schottenfeld et al.[45] No difference at 5 years was noted; however, the overall survival rate at 10 years was 40% for men, compared with 62% for women. This difference in 10-year survival rates was limited to stage II patients with positive nodes; the 10-year survival rate of males with stage I (T1, N0, M0) disease was 89%, the same as in women. In this study, there were similar percentages of patients with pathologically negative nodes (46% *versus* 48%), similar involvement of level I nodes (17% *versus* 19%), and level II to III nodal involvement (28% *versus* 32%). Rosen and colleagues[46] have shown a close correlation between the highest level of axillary node involvement and the total number of metastatic nodes. Therefore, this difference in survival rate of stage II male and female patients is probably not due to an increased number of involved nodes in men.

Based on the acceptable survival rate among node-negative male patients, we do not advise adjuvant therapy in this subgroup.

Our survival data at 5 years are very similar to 5-year data reported for women treated with mastectomy. Patients in the mastectomy arm of the National Surgical Adjuvant Breast Project (NSABP) B-06 trial, comparing modified radical mastectomy with breast conservation therapy, had a 66% 5-year relapse-free survival and a 76% overall (5-year) survival.[47] These figures closely match survival figures in our series of male patients.

We would agree with Crichlow et al.,[48] who have suggested that the central location of all male breast cancers in the presence of pathologically involved axillary nodes theoretically increases the likelihood of internal mammary lymph node involvement. To our knowledge, these nodes have not been evaluated or treated in any systematic manner, and the current study is no exception. Only one patient in our study underwent extended radical mastectomy, and his internal mammary nodes were negative. None of the initial (locoregional) recurrences were internal mammary node recurrences. Our present policy is to advise all male breast cancer patients with positive axillary nodes to undergo adjuvant systemic therapy. It would not seem unreasonable to add radiation therapy to the internal mammary lymph node chain in patients with central and inner quadrant lesions.

Summary

Male breast cancer is evaluated and managed in a very similar fashion to that for female breast cancer. Clinical gynecomastia does not seem to be associated with the development of breast cancer. Mammography is less useful than in women because of small breast size, but should be done to evaluate the contralateral breast. Primary management in early stage disease is most often a modified radical mastectomy. Breast preservation is usually not an option because of small breast size and the absence of the psychological problems attendant to mastectomy in women. No firm recommendations can be made concerning adjuvant systemic therapy; however, it is likely that studies from female patients are adaptable. If administered, chemotherapy similar to that used for female breast cancer is selected. Doxorubicin and alkylating agents are the most active drugs in the limited studies available. First-line hormonal therapy for metastatic disease in our institution is tamoxifen for estrogen-receptor–positive patients. Second-line therapy consists of progestins or antiandrogens/luteinizing hormone–releasing hormone analogs (buserelin). Third-line therapy consists of orchiectomy and, possibly, aminoglutethamide.

The current study documents better survival figures than have been historically reported for male breast cancer patients, and these may be a reflection of significantly reduced delay in treatment. The survival figures reported are similar to currently accepted figures reported for female breast cancer. Moreover, as is the case with female breast cancer, on multivariate analysis the most powerful predictor of outcome in men is the status of the axillary lymph nodes. The only prognostic factor that adds significantly to the predictive power of the axillary nodes is the duration of symptoms. Patients who sought treatment in less than 6 months after the onset of symptoms experienced a significant survival advantage when compared with patients whose symptoms were present for more than 6 months.

In conclusion, carcinoma of the male breast is remarkably similar to carcinoma of the female breast. The similar natural history of the two diseases suggests that breast cancers in women and men share a common origin. It also would appear that the poor prognosis reported in previous studies has given way to improved public and medical awareness of the disease, and, specifically, to an awareness of the benefits of prompt diagnosis and the institution of therapy at a stage when cure may be possible.

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DISCUSSION

DR. EDWARD M. COPELAND III (Gainesville, Florida): Dr. McKinnon, congratulations to you and your colleagues on an excellent paper. It represents a large series of male patients that were treated during modern times and from which some definitive conclusions can be drawn. The paper supports my bias of many years that the same prognostic factors should be used for both male and female breast cancer, and that the survival rate for male breast cancer is worse because the disease is initially diagnosed at a later stage in men than in women.

Now having said this, I was surprised at the 15% incidence of carcinoma *in situ* and the 48% incidence of both invasive and *in situ* disease together in the same specimen. In women, *in situ* disease is often diagnosed by mammography. I would ask the authors to elaborate in more detail about the symptoms, diagnosis, and biopsy techniques for *in situ* disease in this series. The authors deleted patients from the series who presented with distant metastasis. Presentation with distant metastasis in men is particularly unusual. How many such patients were there? Fourteen per cent of the patients had a family history of breast cancer. What recommendations, if any, should be given to men who have several first-degree relatives with breast cancer?

I had access to the manuscript, and there are some data in the manuscript that are equally as interesting as the data that Dr. McKinnon presented. For example, I was intrigued that most of the tested patients were both estrogen receptor (ER) and progesterone receptor (PR) positive, and that responses in metastatic male breast cancer had been achieved with tamoxifen. The authors mention that tamoxifen is their first-line drug for metastatic disease in ER-positive patients. Is this true regardless of the patient's age?

Finally, I would agree with you, Dr. McKinnon, and at least one of your co-authors that neoadjuvant chemotherapy followed by surgery and radiation therapy is the treatment of choice for advanced male breast cancer. Likewise, I would recommend radiation therapy, as do you, to patients who have central and inner quadrant lesions. I would use radiation therapy to the internal mammary lymph nodes, as you suggest in your manuscript. Thank you for the opportunity to discuss the paper.

DR. RICHARD G. MARTIN (Houston, Texas): Dr. Bland, Dr. Jones, Members and Guests, I certainly did enjoy this paper. And it is a very interesting subject, especially when you hear so much about breast cancer at this time, especially in the woman. We have had at the M. D. Anderson Hospital, since 1944, 215 cases of male breast cancer; however, only 72 of those have been treated entirely at our institution. A lot of them in the early years came after they had been treated and had recurrences, and it was up to us to treat the metastases. We agree wholeheartedly that we should attack these very similarly to the female breast.

I think that we need to look into the hormone area a little bit. I did not have the privilege of reading the paper, so Ted brought out some of the things on the hormones, and certainly we have found that tamoxifen is a good drug. It is interesting as far as family history is concerned. I was interviewing a female breast patient a couple years ago, and I asked if she had any family history — her mother, sisters, grandmother, aunts, cousins — and she said "no." A couple days after I had operated on her, she said, "I made a mistake." She said, "I didn't tell you that my father's brother had breast cancer." So I think that that is intriguing, and I think that we need to look into that: whether the male breast patient can influence the female breast patient and vice versa. I think those are very important.

I also would be interested to hear how they use mammography, especially in patients with gynecomastia in that age group that might have malignancy, and also whether ultrasound and fine-needle aspiration biopsies are used. Thank you.

DR. ROBERT M. BEAZLEY (Boston, Massachusetts): Thank you, Kirby. Dr. McKinnon, I enjoyed your paper, and when I saw the abstract, it reminded me of an experience that I had before leaving New Orleans, which constituted a review of experience in male breast cancer up until about 1982 in the Charity Hospital tumor registry and a few patients culled from the VA hospital. I would like to just briefly present a historical perspective at this point. There were 57 patients, with an average age of 63 years. Roughly 24%, or 13, were classified as stage I. Most patients were treated with radical mastectomy, with an overall 5-year survival of 64%. More than half were stage II, with positive nodes, and the 5-year survival for those patients was 30%. There were no survivors for what we classified as stage III, which constituted about one fourth of the total group. The overall survival rates for breast patients, both men and women, were compared, and we had 3300 female patients who had had mastectomies. Of the stage I group, 74% were 5-year survivors. Comparing that with our male breast group, 64% were 5-year survivors. In the stage II group, the numbers were almost the same, 38% and 30%. I think we came to the conclusion then that this was essentially the same disease as female disease and should be treated in roughly the same manner.

My question for you concerns the use of radiology in these patients; most of the patients I see who have gynecomastia come in with a mammogram in hand, and somebody chuckling about it because it was technically very difficult to do. I am curious as to whether your radiologists called your mammograms positive for cancer or were they positive for "a mass"? Is it necessary to treat all patients with gynecomastia with some type of surgical procedure based on what you have learned from your review? Thank you. I enjoyed your paper.

DR. VERNON H. REYNOLDS (Nashville, Tennessee): Dr. Bland, Members and Guests, I would like to congratulate Dr. McKinnon and his coauthors on a very fine and informative paper. I thought it would be appropriate with such a rare tumor to add still another experience. Last year we reported 41 cases of male carcinoma of the breast from the Vanderbilt-affiliated hospitals. This was from a 37-year period, 1950 to 1987, again testifying to the rarity of this entity. Interestingly, 12% of our men had gynecomastia, and 8% had a family history of breast carcinoma. Stage for stage, our male patients had the same 5-year survival as women with breast carcinoma. Our stage I patients at 5 and 10 years had 100% survival. Ten of our patients in the latter part of the study — in the years when our determination of ERs were available — were all positive, 100% positive. And I would like to suggest in view of this high frequency of positive hormone receptors that tamoxifen may gain increasing importance as the first-line adjuvant therapy for most male patients with carcinoma of the breast. Again, I would like to thank the authors for the privilege of the floor.

DR. PATRICK I. BORGEN (Closing discussion): Dr. Ochsner, Dr. Bland, Dr. Jones, and Members of the Southern Surgical, I would like to express my sincere gratitude this afternoon for the privilege of the floor. I also would like to thank the other discussants for their excellent questions.

With respect to Dr. Copeland's remarks, just before I close, I am going to show you a slide on some new and upcoming prognostic factors at the genetic level that seem to be identical in both the male and the female form of the disease. I promise I did not put Dr. Copeland up to that question.

With respect to your question about the diagnosis of *in situ* disease in men, half of these presented as Paget's disease of the nipple, and the other half were macroscopic palpable Paget's disease. None of these were picked up on screening evaluations. I do not have a denominator for you on the patients that presented with distant metastatic disease and were eliminated from this study.

As for your question about recommendations for the relatives of these patients, we have a high-risk special surveillance clinic. This is offered to the relatives of male patients with breast cancer. We try to obtain accurate pedigrees on all of these patients. Sometimes it is difficult. I think that that is a ripe area for further study. In previous years, Drs. Kinne and Hakes have reviewed the experience with hormonal manipulation in males with disseminated disease. And as alluded to by one of the other discussants, there's a very high rate of ER-positive, PR-positive tumors in male breast cancers. Among those patients, there is a very high success rate of both partial and complete responses with drugs such as tamoxifen. In our study, we only had seven patients who received tamoxifen in the adjuvant setting, and one of those patients had a systemic failure.

With respect to Dr. Martin's question about how we use mammography, if you eliminate the screening component of mammography, we use it exactly as we use it in female breast cancer. It is used primarily to evaluate the contralateral breast. In our series today, two of the 100 patients had a synchronous bilateral tumor.

I appreciate Dr. Beazley's remarks for a historical perspective. We had twice as many stage I patients in our group. He had 13%. And our overall survival rate was better than 80%, compared with 65%. So things are getting better with time; it is becoming more like the female form of the disease. When you see a patient with gynecomastia, I think that you cannot overemphasize the importance of an accurate history. A drug history is critical. An examination for things such as testicular masses is also important. We also are in the habit of performing fine needle aspirations for cytologic study of these masses. And if these cells are class 1, no atypia, we often do not recommend biopsy.

I have two concluding points that I would like to make that address the comparisons we have talked about this afternoon between male and female breast cancer. First of all, the ratio of female-to-male breast cancers has changed significantly over the past 15 years. We are all quite aware of the dramatic increase in the incidence of female breast cancers, increasing from 87,000 cases in the United States in 1977 to 175,000 cases this year. The incidence of male breast cancers has remained steady at 900 cases per year. The ratio of women to men has gone from 100:1 before to 1975 to 200:1 this year. To examine where this increase has occurred, we looked at age-specific female-to-male ratios, first from the Connecticut Tumor Registry over the period 1950 to 1965. During that period and over all age groups, the ratio remains steady at 100 female cancers to 1 male. From the years 1970 to 1979, in the Seer group, the ratio went to 550:1 in the 35- to 40-year-old age group and is well above a 100:1 ratio for all ages below 60. Therefore, it appears that at least part of the increase is due to an increased incidence of breast cancers in young women that has not been accompanied by an increase in breast cancers in young men.

My second point concerns similarities between male and female breast cancers at the genetic level. For this comparison, we turn to an ongoing genomic screening project in our laboratory. We evaluated 32 male breast cancer specimens for the status of five genes that have been studied extensively in female breast cancer. The HER-2/*neu* oncogene, amplified in 25% of women at the DNA level is amplified in 20% of men with breast cancer. The estrogen-responsive gene pS-2, described by Pierre Chambon, rarely amplified, 10% of women, 5% of men. The mutated form of the c-Harvey-*ras* oncogene and the interrelated protein gene (IRP), both so critical in *in vitro* studies and in animal models, appear to play no role at the DNA level in either of these diseases. And, finally, the NM23 gene, a potential metastasis suppressor gene, described by Patricia Stieg from the NIH, we are talking about allelic deletion rather than amplification at the DNA level. In women, 50% of patients have both alleles we can see on Southern blotting. These cases we consider to be evaluable. And in those 50%, there's a 25% rate of loss of one or both copies of the gene. And, interestingly, this same profile is seen when we evaluated male breast cancers. Although we agree that the numbers are small and that no gene has been sufficient to describe the malignant phenotype of either male or female breast cancer, it is intriguing that such similarities exist at the DNA level for these five vastly different genes. And, finally, collaborative efforts such as this one between Memorial Sloan-Kettering and the Ochsner Clinic continue to play an important role in increasing our knowledge of rare diseases such as carcinoma of the male breast. Thank you very much.

Total IgE in Plasma is Elevated After Traumatic Injury and is Associated With Sepsis Syndrome

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Gamma E immunoglobulin (IgE) is associated with allergic reactions, but has not been described as being activated after trauma or sepsis. Total plasma IgE concentrations were determined in 32 patients with major traumatic injury, 29 patients undergoing elective abdominal operations, and 30 healthy volunteers. Mean total IgE concentrations were 271.7 ng/mL, 52.3 ng/mL, and 41.3 ng/mL, respectively ($p < 0.01$ for each comparison with the trauma group). Total IgE concentrations in trauma patients at the time of admission were not significantly different from elective surgical controls, and tended to increase during the intensive care unit stay. In the trauma group, total IgE concentration was significantly greater in the 18 patients that developed sepsis syndrome compared with those that did not ($p = 0.034$). These data suggest that allergic mechanisms may be involved in the physiologic response to major traumatic injury and sepsis syndrome, or that other cells known to be involved in the immune responses to trauma and sepsis (macrophages, platelets, and B lymphocytes) may become activated by IgE-dependent mechanisms.

THE IMMUNE CONSEQUENCES of major traumatic injury are not fully understood; however, most components of the immune system are involved to some extent in the pathophysiologic processes accompanying trauma. It is clear that trauma predisposes patients to sepsis syndrome and multiple organ failure. The responsible mechanisms often involve the interaction of bacteria or bacterial products with the immune system. A well-studied process is macrophage activation after endotoxemia. The activated macrophage releases various mediators including tumor necrosis factor (TNF), interleukin-1, and interleukin-6. These mediators are responsible for end organ effects such as adult respiratory distress syndrome (ARDS), cardiovascular instability, coagulopathy, and renal and hepatic failure.[1]

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The potential involvement of allergy-related or gamma E immunoglobulin (IgE)-dependent immune system activation in the response to trauma or sepsis syndrome has not been adequately investigated. Jacobs and associates[2] measured blood histamine concentrations in patients with nontraumatic septic shock and found that histamine concentrations were not elevated. They therefore concluded that histaminemia was unlikely to play an important role in the pathogenesis of septic shock in humans.

Several IgE-mediated mechanisms may be responsible for the activation of inflammatory cells, resultant mediator release, and eventual organ dysfunction. Allergic mechanisms may be activated if the patient is exposed to allergen concurrent with IgE-sensitized basophils and mast cells. Activation of these cells may cause the release of preformed mediators, and generation of additional allergic mediators, including TNF.[3] Monocytes, eosinophils, platelets, and B lymphocytes may be activated through IgE bound to low-affinity IgE cell membrane receptors.[4]

This study was conducted to determine if total plasma IgE was elevated in patients after major traumatic injury, and to determine if plasma concentrations of IgE were associated with sepsis syndrome, ARDS, renal failure, splenectomy, or death. Patient plasma specimens that had been previously collected and stored by the investigators were used for analysis.

Methods

Patients

Plasma samples from three adult subject groups were analyzed. Group I patient plasma specimens had been

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collected for a previous study and were stored frozen at −20 C. The previous investigation compared the effectiveness of intravenous purified fibronectin with placebo in preventing sepsis.[5] Group I consisted of 32 patients who experienced major traumatic injury from January of 1986 through February of 1989 and were admitted to the trauma intensive care unit at the Medical College of Georgia. Patients with burns or lethal head injury were excluded. The patients ranged in age from 18 to 55 years and were a subset of a 72-patient group previously reported.[5] All patients had an American College of Surgeon's hospital trauma index of 10 or greater. Patients dying within 7 days of admission to the intensive care unit or remaining in the intensive care unit for less than 72 hours were also excluded.

These 32 selected trauma patients included all 18 patients of the 72-patient group who experienced a septic event, and 14 nonseptic patients with similar lengths of stay in the trauma intensive care unit. Characteristics of this patient group are presented in Table 1. A plasma bank was established for these patients, consisting of one to three daily specimens for the entire length of stay in the intensive care unit.

In the traumatically injured patient group, septic patients most frequently developed infections in the bloodstream or lower respiratory tract. Bacteremia was observed in 14 patients; lower respiratory tract infection, in seven patients; and wound infection, in one patient. Sepsis syndrome was associated with gram-negative bacteria in 10 patients, gram-positive bacteria in three patients, and a mixture of gram-negative and gram-positive bacteria in five patients. The most common isolate from blood was Enterobacter species (six patients).

TABLE 1. *Characteristics of Patient Groups*

Traumatically injured patients (group I)	
N	32
Mean age (SD)	33 ± 8
M/F	29/3
American College of Surgeons score	13.9 ± 2.9
Range	10–22
No. with	
Sepsis syndrome	18 (56%)
ARDS	20 (63%)
Renal failure	11 (34%)
Splenectomy	9 (28%)
Death	8 (25%)
Elective surgery patients (group II)	
N	29
Mean age (SD)	51 ± 16
M/F	16/13
Indication for operation	
Colon cancer	14
Colostomy closure	5
Gastric surgery	5
Pancreatic/biliary disease	4
Other	1
Healthy volunteers (group III)	
N	30
Mean age (SD)	31 ± 9
M/F	14/16

ARDS, adult respiratory distress syndrome.

Group II consisted of 29 patients who underwent an elective abdominal operation during 1988 (Table 1). The mean age of this group was greater than the comparative groups. Venous blood samples were collected at the time of closure of the surgical incision. The initial intent of blood collection in these patients was to determine plasma antimicrobial concentrations in a surgical wound prophylaxis study. Group III consisted of 30 heathy volunteers who were hospital employees. Allergy histories were not available for any of the patient groups except that patients in group II could not have had a history of immediate or life-threatening reaction to beta-lactam antimicrobials.

Total Immunoglobulin Determinations

All plasma samples were stored at −20 C until assay. Total IgE concentration was determined on blinded specimens by an automated microparticle enzyme immunoassay (IMx, Abbott Diagnostics, North Chicago, IL). The lower limit of detection of this assay is 0.1 ng/mL. Within-run and between-run coefficients of variation over the 0.1- to 480-ng/mL range were <3%. Specificity has been confirmed using purified IgE, IgM, IgG, and albumin. For group I (trauma patients), total IgE was measured in three or four separate plasma samples from each patient. The first sample was selected from plasma collected less than 24 hours after admission. Additional samples were chosen for analysis at approximately weekly intervals during the intensive care unit stay. For groups II and III (elective surgery and normal controls, respectively), plasma samples were obtained only once, and these were used for total IgE determination.

Total IgG and IgM were determined two to three times weekly during the intensive care unit stay for group I patients only. These were assayed by rate nephelometry (Behring Diagnostics, Inc, Somerville, NJ). The lower limits of detection are 170 mg/dL for IgG and 25 mg/dL for IgM. The within-run and between-run coefficients of variation were 2.5% and 3.2% for IgG and 2.3% and 4.3% for IgM. The 95% confidence interval for normal range was 760 to 2150 mg/dL for IgG and 44 to 344 mg/dL for IgM.

Clinical Definitions

The following definitions were used for clinical events. Sepsis syndrome was determined by a combination of clinical signs and symptoms, as well as physiologic and laboratory data. Sepsis syndrome was defined as hypothermia (temperature < 35 C) or hyperthermia (temperature > 38.5 C), tachycardia (>120 beats/minute), and tachypnea (>20 breaths/minute), with clinical evidence of an infection and at least one end organ demonstrating inadequate perfusion or dysfunction, expressed as poor or altered cerebral function, hypoxemia (arterial $PO_2 < 75$ mmHg), elevated plasma lactate, or oliguria (urine output <0.5 mL/kg/hour).

Adult respiratory distress syndrome was defined as acute respiratory failure demonstrated by an arterial PO_2/fraction inspired oxygen ratio <200 with bilateral pulmonary infiltrates on chest x-ray, and no evidence of heart failure (pulmonary capillary wedge pressure < 18 mmHg). Renal failure was defined as an increase in serum creatinine of at least 50% from a normal baseline in the absence of hypovolemia.

Data Analysis

Comparisons between groups for total IgE were performed by t test or analysis of variance for log-transformed values. A p value of less than or equal to 0.05 was accepted as significant. All mean total IgE data are presented as the geometric mean.

Results

Mean total IgE data are presented in Table 2. The mean total IgE concentrations were significantly greater for the trauma patients (group I) as compared with either of the control groups (II and III). Also, there was no significant difference between groups II and III. Frequency distributions of total IgE data expressed as percentiles of the nonallergic control population that was used to establish normal ranges for the IgE assay are shown in Figure 1. The mean percentiles for groups I, II, and III were 85.8, 46.3, and 47.9, respectively.

The plasma concentrations of total IgE in trauma patients were further analyzed. To determine if total IgE increased during the intensive care unit stay, the highest total IgE was compared with the initial (first 24 hours) total IgE for each patient. The mean initial total IgE was 100.3 ng/mL (range, 3.5 to 1336 ng/mL) (Fig. 2). The mean initial total IgE from group I was significantly different from the mean highest observed total IgE for that same group of 271.7 ng/mL ($p = 0.0023$). The mean initial total IgE concentration for group I, however, was not sig-

TABLE 2. *Mean Total IgE Concentrations*

Group	Mean IgE (ng/mL)* (95% confidence interval)	Significant Difference for Comparative Groups ($p < 0.01$)
I Trauma patients	271.7 (156.0 to 473.4)	II and III
II Elective surgical controls	52.3 (24.8 to 80.6)	I
III Healthy controls	41.3 (21.8 to 69.4)	I

* For group I, the highest observed value for each patient was used, whereas for groups II and III, only one observation per patient was included.

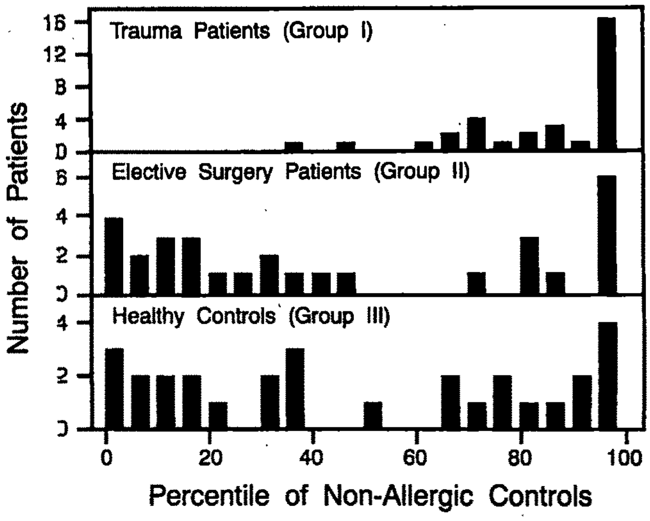

FIG. 1. Percentile distributions for total IgE concentrations for groups I, II, and III.

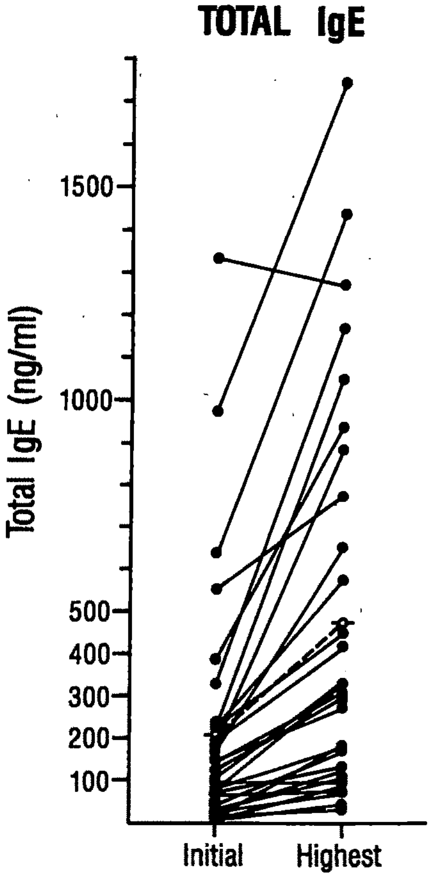

FIG. 2. Changes in total IgE concentrations from admission value to highest observed value for individual patients from the trauma group (group I) (with means noted by open circles) ($p = 0.0023$).

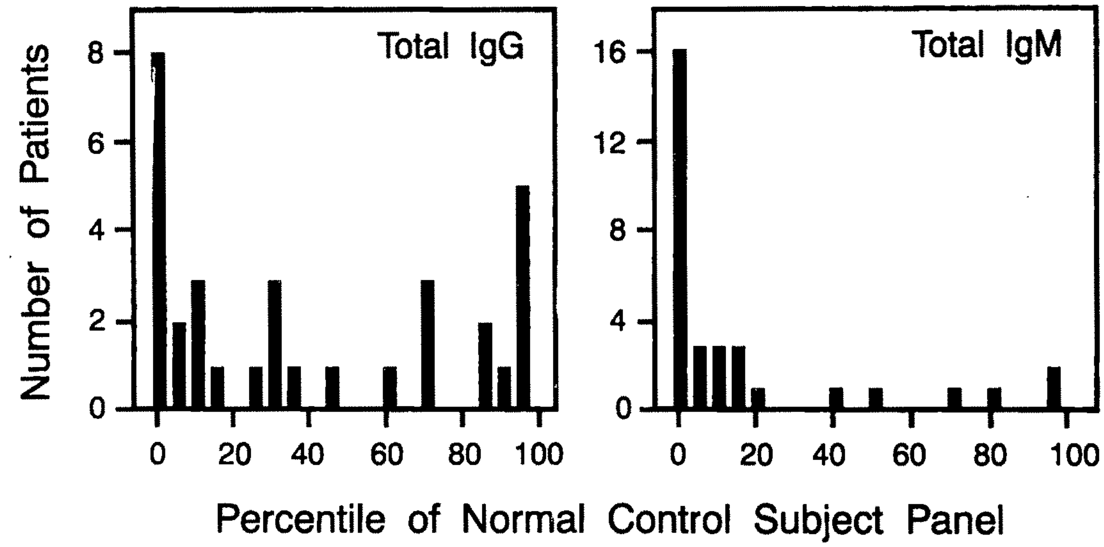

FIG. 3. Percentile of normal control group for total IgG and IgM determinations in trauma patients (group I) at time of highest observed total IgE concentration.

nificantly different from the mean total IgE in surgical control patients (group II, 52.3 ng/mL) (p = 0.135), but was significantly different from the mean total IgE in the normal controls (group III, 41.3 ng/mL) (p = 0.035).

Total plasma IgG and total IgM concentrations were determined for the trauma patients (group I) during their intensive care unit stay. For each highest observed total IgE, total plasma IgG and IgM concentrations were available for samples collected within 48 hours of the total IgE samples. The mean total IgG and IgM values (± standard error of the mean) corresponding in time to the total IgE determinations were 1336.1 ± 125.1 mg/dL and 109.5 ± 18.9 mg/dL, respectively. The percentile distributions based on a normal control population of 120 hospital employees are presented in Figure 3. Gamma G immunoglobulin values were extremely variable, approximating a bimodal distribution, with the peak frequencies occurring in the 5th and 95th percentiles. In contrast, total IgM values were skewed to the lower percentiles, with 25 of 32 observations below the 20th percentile.

Relationship to Clinical Events

Total IgE values were analyzed in relation to the occurrence of important clinical events in group I patients. The results of this analysis for the incidence of sepsis syndrome, ARDS, renal failure, splenectomy, and death are presented in Table 3. Mean total IgE concentrations (highest observed) were significantly greater (p = 0.034) in septic patients. Mean total IgE concentrations were higher in patients with ARDS, renal failure, splenectomy and in those who expired, but were not significantly different from the subset not experiencing the specific event. For 12 of the 18 septic patients, the highest total IgE observed was from the plasma sample collected closest to the time of the onset of sepsis syndrome. In five patients, the highest total IgE was observed after the resolution of sepsis syndrome, and in one patient the initial value was the highest value observed.

Discussion

The findings of this study demonstrate that total IgE plasma concentrations were increased in patients with major traumatic injury. Mean total IgE concentrations were significantly greater in septic patients compared with nonseptic patients. Although not significant, there was a

TABLE 3. *Relationship Between Highest Observed Total Plasma IgE Concentration and Clinical Events in Trauma Patients (Group I)*

Event	N	Mean Total IgE (95% confidence interval)	p
Sepsis			
Yes	18	388 (235 to 639)	0.034
No	14	172 (98 to 302)	
ARDS			
Yes	20	331 (202 to 539)	0.195
No	12	196 (104 to 372)	
Renal failure			
Yes	11	432 (226 to 829)	0.083
No	21	213 (133 to 340)	
Splenectomy			
Yes	9	330 (156 to 699)	0.537
No	23	252 (158 to 403)	
Death*			
Yes	8	304 (136 to 679)	0.745
No	24	262 (164 to 416)	

* While in the trauma intensive care unit.

trend toward elevated total IgE concentrations with organ dysfunction (ARDS and renal failure).

Excluding patients who died within 48 hours of injury, the 32 trauma patients selected for this study were among the most severely injured of approximately 3600 total admissions to the trauma service during the study period. The severity of injury is supported by the high percentage of patients experiencing organ dysfunction and death.

Increased plasma IgE could be the result of increased production, decreased degradation, or release from an IgE pool (such as low-affinity IgE Fc receptors on monocytes); however, the mechanism of IgE disregulation cannot be determined from this study. Increased IgE concentrations over a period of weeks in some patients suggest that the latter mechanism is unlikely. Also, it is not clear whether elevated IgE concentrations in this setting are a cause or effect of cellular and organ dysfunction that accompanies traumatic injury. It is possible that changes in IgE concentrations resulted from fluid shifts, although low to normal serum albumin and total IgM values suggest that hemoconcentration is unlikely.

In recent years, several mechanisms of IgE regulation have been elucidated.[6,7] A major upregulator of IgE production in human and murine systems is interleukin-4 (IL-4). More recently, IL-6 has been recognized as an enhancer of IL-4–induced IgE production.[6,8] Another mediator involved in IgE production is interferon gamma. Interferon gamma appears to be an inhibitor of IL-4 and IgE synthesis.[6,9] In fact, increased production of IgE may be an indicator of imbalance between IL-4 and interferon gamma production.[6,10,11] Hyper-IgE syndrome has been associated with defective production of interferon gamma.[11,12] In the setting of trauma and sepsis syndrome, increased IL-4 activity may not only increase IgE production but also may suppress interferon gamma production[9,13,14] and inhibit monocyte release of other important mediators such as TNF-α, IL-6, and IL-1.[13,15–17] Whether the overall effect of IL-4 is protective or detrimental is not yet evident.

The dichotomy of cytokine secretion and IgE production is relatively distinct in the murine system, where most CD4+ lymphocytes can be classified as T_{H1} (preferentially producing interferon-gamma, IL-2, and TNF-β) or T_{H2} (preferentially producing IL-4, IL-5, and IL-6).[18] In the murine system, T_{H2} clones have been demonstrated to promote IgE production and inhibit cell-mediated immunity. In normal humans, this distinction is not as apparent; however, subsets of T_H cells with differing cytokine production do exist.[19] In patients with hyper-IgE syndrome[12] and *Mycobacterium leprae* infections,[13] preferential cytokine production for T_H subsets has been demonstrated.

A number of independent findings in traumatized and septic patients suggest that increased IgE production may be favored. Promoters of IgE production (particularly IL-6) are reported to be increased after trauma and sepsis in humans.[15,20,21] An inhibitor of IL-4–induced IgE production, interferon gamma, is decreased.[22–24] Other inflammatory products demonstrated to enhance IL-4–induced IgE production, such as prostaglandin E_2, are increased.[15,23,25] Prostaglandin E_2 also may favor production of T_H cells preferentially, producing IL-4, IL-5, and IL-6.[26] Also, of interest, corticosteroids have been demonstrated to enhance IL-4–induced IgE production,[27] and the stress response in general may favor IgE production.[28] Interleukin-4 has not been well studied in the setting of trauma and sepsis, but may be important because, in addition to being a major inducer of IgE production, it is involved in attenuating macrophage production of TNF-alpha and other mediators.[13,15] Also, IL-4 activation may partially explain depressed cell-mediated immunity which has been well documented after traumatic injury.[29,30] Increased IgE may be the result of the altered cytokine environment in trauma patients, and this may be an effect, as opposed to a cause, of sepsis and organ dysfunction.

There are at least two potentially important implications of elevated IgE in traumatized and septic patients. First, the possibility exists that allergic mechanisms may be involved in the physiologic response to major traumatic injury. Activated basophils and mast cells may not only release preformed and newly generated mediators of allergy, but also may be a source of TNF, an important primary mediator of the sepsis syndrome.[3,31] Second, IgE may be involved in activation of a number of other cells, including macrophages, platelets, eosinophils, and B lymphocytes, all of which have low-affinity IgE cell membrane receptors.[32–34] Activation of any of these cells may initiate inflammatory processes that contribute to the development of organ dysfunction.

In conclusion, this is an initial report of elevated plasma total IgE concentrations in patients who have experienced major traumatic injury. Gamma E immunoglobulin concentrations were higher in traumatically injured patients compared with healthy volunteers or patients undergoing elective abdominal operations. Also, total IgE concentrations were higher in traumatically injured patients that developed sepsis syndrome. To more fully understand the implications of elevated IgE concentrations in these patients, it will be necessary to determine the causes of IgE disregulation that accompany trauma and sepsis syndrome, if elevated IgE concentrations result in cell activation, and if this activation is responsible for the organ dysfunction of the sepsis syndrome.

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DISCUSSION

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): Dr. Bland, Dr. Jones, this is an excellent contribution, and I think it is one of the most attractively illustrated talks that I have seen in a long time. I think it is also nice to get Dr. DiPiro's number of contributions in the field of infection linked with Dr. Mansberger's long-time interest in shock and trauma. It begins to pull some things together that many of us have been interested in for a long time. I guess I would favor the authors' second hypothesis that the IgE variations are an effect, rather than a cause, of what is going on in this situation. I suspect it is a function of those cascades of cell-to-cell messengers that are so much a part of our description of response to trauma, operation, and injury today. It is almost impossible, I think, for a person who does not work in this field to keep up with this, and I would suspect most of you ought to wait until it comes out in *Scientific American* in about 10 years and read the comic book version.

Our thoughts are that it may be that lowered endogenous gamma interferon production, which is such a characteristic of both trauma and burns, triggers this whole process. But one has to understand that this is a process of turning on and turning off these agents in sequence. I have said before, and I say again, what we probably need is something like a pulse oximeter for a moment-to-moment kind of measurement of these host defense responses before we will know what is happening in a meaningful way. I therefore would ask my one question that was generated by this presentation. Rather than look at the highest IgE levels, it would be more interesting to see a time course of some of these badly hurt patients, to see how promptly it goes up and how it waxes and wanes with their clinical illness. I believe that would tell us the most under those circumstances, and if you have some of those data, Dr. DiPiro, it would be nice to hear about it. I suspect that this is going to prove to be a valuable bit of information and something in a field that is growing exponentially right now, and I believe it will tell us a great deal about these interactions. I appreciated hearing the paper. Thank you very much.

DR. J. RAYMOND FLETCHER (Mobile, Alabama): Thank you very much, Dr. Bland, Dr. Jones. I really enjoyed the presentation. I think, like Dr. Polk, that this is a new piece of information that is very difficult for us to sort out. And I agree also with Dr. Polk in that the concept of having a temporal relationship to this IgE may be very important. And, as Dr. Mansberger implied, a prospective study would probably be the best to provide that. I raise the question about whether or not this total elevation is truly comparable to the other two patient groups with respect to their intensive care unit stay and all the issues that go on with these complex patients. It would be of interest to identify the subsets of patients in which there might be the greatest change in these values and then make some temporal relationship to control patients under similar kinds of circumstances. I also would like to know what the relationship of these levels were to the patients that had positive blood cultures.

I was surprised to find that only in the septic group of patients were there some correlations or significant differences. Many of the other patients had multiple problems of renal failure, and pulmonary failure. So that is a kind of surprising piece of information because we know that in patients with sepsis there generally is multiple organ failure. I enjoyed this paper very much. I do think the mediators released would be of interest in these particular patients, and I would be curious if you have any of those data. Thank you very much for the privilege to discuss this paper.

DR. BENJAMIN F. RUSH (Newark, New Jersey): Dr. Bland, Dr. Jones, Members and Guests, it is a pleasure to comment on this very nice piece of work, which adds another portion, if you will, to the complex puzzle of the immune inflammatory response after severe trauma and shock. As the previous two discussants, I am rather hesitant to embark on this stew of cytokines into which this particular chain may be leading us.

First of all, the antigen-antibody complex that is stimulated by trauma has been called by some the fuse that ultimately leads to activating the blasting cap, which is usually identified as a macrophage, and then of course the explosion of cytokines that result from that may lead to a lot of the damage that one sees in the traumatized patient. You are looking here of course in terms of a immunoglobulin as an initiator of the complementary chain in most cases. And I ordinarily would anticipate that if you're really interested in this particular chain, one would be inclined to look at IgG first, because 75% of the immunoglobulin is made up of that particular molecule.

IgE has been identified as the particular immunoglobulin that may be more related to allergic reactions, to which the speaker has already referred. Thus, although it may well have an unsuspected role in the whole picture of the traumatized patient, and probably does deserve study, it is probably not the one to look at first.

So I guess that leads me to my first question. Why are you looking at IgE, and what happened to IgM? Although I know that you did measure it, I would like to hear about that.

Finally, we are looking at peaks here. Evaluation of cytokines that are part of a chain of reactions must consider that they are consumed or bound as they are activated, leading not only to peaks but also valleys in the level of concentration over time. So what I am also interested in is, how about the valleys? And finally, I would like to echo what Dr. Polk said: What happened over time? What did we see right at the initiation of the trauma and then perhaps later on during the course of the trauma to the patient? At any rate, it looks to me as though this does open up a new set of doors, and I will look forward to your future reports. Thank you very much.

DR. JOSEPH T. DIPIRO (Closing discussion): Thank you, Dr. Bland. I would like to thank our discussants for their comments and questions.

First of all, regarding the time course of IgE elevation, we did not have daily levels measured, and so our conclusions regarding the time course are limited. For the septic patients, we did observe that in 12 of 18 patients the highest total IgE observed was from the plasma sample collected closest to the time of the onset of sepsis, which was generally within 48 hours. In five patients, the highest total IgE was observed after the resolution of sepsis, up to 10 to 14 days later, and in one patient the initial value collected in the emergency room was the highest value observed. Regarding the control groups, for our healthy controls and our elective surgery controls, we only had access to one sample for each patient. And in our healthy controls, we assumed that their IgE levels would be stable. We believed it more important to have samples that were available and stored under the same conditions, that is, frozen for a similar time as opposed to collecting new fresh samples.

Regarding information on the types of infections that these patients had, for the septic patients, bacteremia was observed in 14 patients, lower respiratory tract infections in seven patients, and wound infection in one patient. The sepsis syndrome was associated with gram-negative bacteremia in 10 patients, gram-positive infections in three, and a mixture of gram-negative and gram-positive in five patients. We have no data on mediator release. We were not sure of the stability of the mediators in frozen serum and chose to look at this in a prospective fashion.

Why did we select IgE? We found that this isotype has not been adequately studied in the setting of trauma. IgM and IgG have been examined, and it is known that IgM is depressed after injury and sepsis. We could find nothing that addressed IgE, and theoretically a mechanism was available whereby it may participate in this process, so we thought it was important to examine.

Regarding the lowest IgE levels, given our limited data, there is not much that we can say other than that the initial levels that were collected on presentation to the emergency room were lower than those observed later during the ICU stay and were significantly different from our surgical controls.

Finally, I would like to thank the members of the Association for the privilege of discussing our paper.

Abdominal Packing For Surgically Uncontrollable Hemorrhage

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Planned intra-abdominal packing for surgically uncontrollable hemorrhage from liver and retroperitoneal injuries exacerbated by hypothermia, acidosis, and coagulopathy regained popularity over the past decade. The authors reviewed 39 patients injured between August 1985 and September 1990; 31 packed for liver injuries, eight for nonliver injuries. The overall mortality rate was 44% (17/39); 9 (23%) exsanguinated, 3 (8%) died of head injuries, 3 (8%) of multisystem organ failure, 2 (5%) of late complications. The mean age was 33.9 ± 16.2 (range, 16 to 79); there were 26 men and 13 women. Relaparotomy for pack removal was performed 2.0 ± 1.1 days (range, 1 to 7) after initial operation. The authors identified intraoperative risk factors of pH ≤ 7.18, temperature ≤ 33 C, prothrombin time ≥ 16, partial thromboplastin time ≥ 50, and transfusion of 10 units or more of blood as highly predictive of outcome. Patients with four to five risk factors ($n = 3$) had a 100% mortality rate ($p < 0.04$); two to three risk factors ($n = 12$), 83% mortality rate ($p < 0.003$), compared with zero to one risk factors ($n = 24$), 18% mortality rate. Complications developed in six of 22 survivors (27%): 5 abdominal abscesses (23%), 2 wound dehiscences (9%), and 2 enterocutaneous fistulae (9%). Intra-abdominal packing will not stop all bleeding; 23% of the patients exsanguinated. In 77%, packing helped achieve hemostasis we believed was not otherwise possible. Packing may be done to prevent the development of acidosis, hypothermia, and coagulopathy or may be done early in the treatment of cold, acidotic patients rather than massive transfusion in the face of surgically uncorrectable bleeding.

THE CONTROL OF severe hemorrhage in the face of hypothermia, acidosis, and coagulopathy is a formidable problem for even the most experienced trauma surgeon. Planned perihepatic and intra-abdominal packing in such patients may be life saving and has regained popularity in the last decade.[1,2] Packing as an adjunct to surgical techniques of resectional debridement, hepatotomy and selective vascular ligation, prolonged portal inflow occlusion with a Pringle maneuver, and vascular isolation techniques is widely accepted. Packing before definitive surgical repair at a planned reoperation is another alternative for patients undergoing exploration who are unstable or in whom the surgeon judges further blood loss to be untenable.[3]

Planned packing for nonliver injuries uncontrolled by standard surgical techniques is also practiced. The patient with a severe pelvic fracture whose retroperitoneal hematoma ruptures or who is surgically entered may only be surgically salvageable with planned packing.

The critical events leading to the decision to pack are usually recognition of severe hepatic injuries that continue to bleed after numerous surgical techniques and the development of coagulopathy. The timing of the decision to pack is controversial: should packing be instituted before development of coagulopathy, and therefore a large number of patients are packed, or should packing be delayed until the onset of coagulopathy, thereby lessening the number of patients packed but possibly decreasing the salvage rate? We have reviewed our experience with intra-abdominal packing for control of surgically uncorrectable hemorrhage over a 5-year period to review the impact of hypothermia, acidosis, and coagulopathy on success of packing.

Materials and Methods

The records of 39 adult patients undergoing perihepatic or intra-abdominal packing at Vanderbilt University Hospital between August 1985 and September 1990 were reviewed. Records were reviewed for demographic data on patient age, sex, and major diagnosis. We tabulated hospital stay, grade of liver injury (using the classification

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TABLE 1. *Liver Injury Classification Scale*

Grade	Liver Injury
1	Capsular avulsion Parenchymal laceration <1 cm deep
2	Parenchymal laceration <3 cm deep Subcapsular hematoma <10 cm
3	Parenchymal laceration >3 cm deep Large subcapsular hematoma, <10 cm Central penetrating wound
4	Massive unilobar damage Massive central hematoma
5	Retrohepatic vena cava injury Hepatic venous injury Massive bilobar destruction

system in Table 1), Injury Severity Score (ISS) and emergency room (ER) and operating room (OR) course. The presence of shock in the ER, transfusion in the ER, coagulation studies done in the ER—prothrombin time (PT) and partial thromboplastin time (PTT)—temperature, and pH were recorded. The OR course, operation performed, outcome, packing and postoperative course were reviewed for mortality rate, day of re-laparotomy for pack removal, and complications. The coagulation studies recorded were performed on the patient's arrival to the ER, usually through a femoral venipuncture, but not through heparinized arterial lines or central venous lines. The lowest pH recorded was from arterial blood gas analysis, and the lowest value measured in the ER or in the OR was recorded. The lowest temperature recorded was the lowest value recorded in the ER or OR.

Operative technique for management of liver injuries included exposure through long midline incisions and initial tamponade of bleeding by manual compression. Major injuries were managed by mobilization and exposure of the liver followed by such techniques as resectional debridement, tractotomy or hepatotomy with selective vascular ligation, and portal inflow occlusion with the Pringle maneuver. Formal lobar resection, selection hepatic artery ligation, or atriocaval shunt placement were not used in this group of patients. Decision to pack was based on the surgeon's opinion that coagulopathy had developed and nonmechanical hemorrhage was present or that the patient was too unstable to undergo further blood loss. Ruptured pelvic or retroperitoneal hematomas were packed in unstable patients in whom opening of the hematoma was believed to be futile. Packing was done with laparotomy pads applied directly over the bleeding sites. The abdomen was closed under tension with suture or towel clips to maintain pressure on the packs—no mesh closures were used at the initial operation. Transfusion management consisted of transfusion of 2 to 4 units of fresh frozen plasma and 6 to 12 units of platelets for each 10 units of packed red blood cells transfused. Intraoperative intravenous fluids, blood, and blood products were warmed or infused through rapid transfusion devices with warmers. Relaparotomy was done between 1 and 7 days after operation (usually 2 to 3 days) after cardiopulmonary function, coagulation factors, hypothermia, and acidosis were stabilized or corrected.

Results were analyzed with the use of several statistical methods including Student's t test, chi square analysis, Fisher's exact test, and Pearson's product-moment regression analysis.

Results

We identified 39 patients undergoing perihepatic or intra-abdominal packing for control of traumatic hemorrhage by review of our trauma registry, interview with all attending trauma surgeons, and medical record review. We found 31 patients undergoing perihepatic packing for liver trauma and eight patients packed for control of retroperitoneal or pelvic hematoma bleeding. There were 26 men and 13 women, reflecting a largely young male trauma population. The average age of the patients was 33.9 ± 16.2 years, ranging from 16 to 79. There were 22 survivors and 17 deaths (overall mortality rate, 44%) with death due to hemorrhage in 9 (23%), head injury in 3 (8%), multiple organ system failure in 3 (8%), and 2 late deaths (5%), 1 due to a myocardial infarction and 1 due to exsanguination from a tracheo-innominate fistula. There was only one patient in the group dying of multiple organ system failure that had an abdominal abscess as the cause of sepsis. These were severely injured patients with an average ISS of 37.9 ± 10.3 (range, 16 to 79). Survivors had an average ISS of 34.7 ± 10.6 (range, 16 to 59), and nonsurvivors had an average ISS of 41.6 ± 8.5 (range, 29 to 79, not statistically different). These patients were massively transfused with an average of 18.9 ± 20.0 units of packed red cells administered in the ER and OR (range, 4 to 88). The deaths due to exsanguination occurred predominately in the OR (5/9, 56%). Three of five OR deaths occurred in patients with cardiac arrest resuscitated before operation in the field with closed chest cardiopulmonary resuscitation, and the other two deaths occurred in patients undergoing resuscitative thoracotomy for profound hypotension. The remaining four deaths due to exsanguination occurred immediately after operation.

TABLE 2. *Mechanism of Injury* vs. *Mortality Rate*

Injury	No. (%)
Motor vehicle accident	9/25 (36)
Gunshot wound	2/6 (33)
Auto pedestrian	4/4 (100)
Miscellaneous	2/4 (50)

Most of the patients were injured in motor vehicle accidents (Table 2). Pedestrians hit by automobiles had particularly lethal injuries, with all four patients needing packing succumbing to their injuries. The miscellaneous injuries included two stab wound victims and two victims of falls.

Analysis of the data comparing survivors with nonsurvivors (Table 3) showed several expected similarities and several unexpected trends. We had expected that nonsurvivors sustaining liver injuries would have had higher-grade liver injuries than the survivors, but the trend was actually the opposite, with survivors having a trend toward worse liver injuries—however, this was not statistically different. The average age and transfusion need in the nonsurvivors was higher, but not statistically different. Importantly, the nonsurvivors had statistically higher ISS scores, lower temperature, lower pH, and significantly worse coagulopathy. Because the PT and PTT were drawn in the ER, they reflect patients coming into the OR profoundly coagulopathic. The lowest recorded pH and temperature in these patients were generally recorded in the OR in these patients and may have reflected the intraoperative development of acidosis and hypothermia rather than the preoperative existence of hypothermia and acidosis. Clearly the existence of preoperative coagulopathy significantly increases mortality rate and likely hastens the development of acidosis and hypothermia by increasing the need for transfusion.

When we examined the mortality rate of the patients with liver injury and stratified them by grade (Table 4), we found the inverse of what we had initially expected. We believed that worse liver injuries would have higher mortality rates and much higher transfusion need. We had one patient with a grade 2 liver laceration (no grade 1 lacerations were packed) who was packed for the liver injury but who died of a subdural hematoma that rapidly progressed. This patient was transferred from an outside hospital acidotic and coagulopathic. We were disturbed to see that mortality rate in the grade 3 liver laceration group was 56% and that these patients required an average of 24.5 ± 28 units of blood. Further analysis of these deaths disclosed that three of the five deaths occurred in the OR in patients with preoperative cardiac arrest, and two deaths were late deaths due to septic complications (including one patient who died 5 days after receiving 88 units of blood for a ruptured descending thoracic aorta, liver laceration, splenic laceration, pelvic fracture, and retroperitoneal pelvic hematoma). One patient with a grade 3 liver laceration from a close range shotgun wound destroying the stomach, tail of pancreas, spleen, splenic flexure of colon, and sustaining epicardial right ventricular lacerations required re-exploration 5 hours after operation for bleeding not controlled by the initial operation. Bleeding points in the liver were oversewn and he was repacked and survived. He illustrates the possibility of salvage in patients continuing to bleed after packing. Patients sustaining grades 4 to 5 liver lacerations had better survival and lower blood transfusion needs, but no intergrade differences were statistically significantly different for either transfusion need or mortality rate.

TABLE 3. *Comparison of Survivors and Nonsurvivors*

	Survivors	Nonsurvivors
No.	22	17
Age	31.8 ± 15.3	36.5 ± 17
ISS	34.7 ± 10.6	41.6 ± 8.5*
Grade liver Injury	4.13 ± 0.70	3.6 ± 0.8
Transfusions	12.4 ± 8.0	21.6 ± 18.3
Lowest temperature	34.4 ± 1.6	32.7 ± 1.9*
Lowest pH	7.24 ± 0.10	7.14 ± 12*
PT	13.9 ± 1.35	34.9 ± 35.8*
PTT	32.5 ± 6.67	85.0 ± 69.5*

* $p < 0.05$.
† $p < 0.02$.
ISS, injury severity score; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 4. *Survival by Liver Injury Grade*

Grade	Mortality Rate No. (%)	Red Blood Cell Transfusion
2 (n = 1)	1/1 (100)	13
3 (n = 9)	5/9 (56)	24.5 ± 28
4 (n = 14)	6/14 (43)	15.7 ± 13
5 (n = 7)	2/7 (29)	14.7 ± 10

We were initially unsure that comparison of patients with liver injuries to patients packed for nonliver injuries would make sense. Patients packed for nonliver injuries were six patients packed for ruptured pelvic hematomas and two patients packed for ruptured perinephric and central retroperitoneal hematomas. The patients with nonliver injuries had many more injuries (Table 5) per patient (an average of 6.2 associated injuries) than did the liver injury patients (2.7 associated injuries). Only significant injuries were tabulated: rib fractures, scalp and facial lacerations, small bone fractures, minor concussions, and minor abdominal injuries such as hematuria, serosal tears, minor mesenteric lacerations, and untreated hepatic and splenic subcapsular hematomas were deemed to have little importance. Comparing data on these patients (Table 6) shows great similarity between the groups. Although the age of patients packed for nonliver injuries was higher (but not statistically different) than patients packed for liver injuries, there were no differences in ISS, transfusion need, temperature, pH, or PTT. The only significant difference was in the admission PT of liver injury

TABLE 5. *Associated Injuries*

Liver Injury (n = 31)*		Other Injury (n = 8)†	
Injury	No.	Injury	No.
Abdominal		Abdominal	
Spleen	8	Mesenteric laceration	5
Colon	4	Colon	5
Kidney	4	Spleen	4
Diaphrgam	3	Stomach	4
Pancreas	3	Diaphragm	3
Duodenum	3	Pancreas	2
Mesentery	2	Kidney	2
Stomach	1	Small Bowel	2
Gallbladder	1	Gallbladder	2
Adrenal	1	Duodenum	1
Small Bowel	1	Aorta	1
Ovary	1	Iliac Artery	1
Skeletal		Vena Cava	
Long bone fracture	11	Skeletal	
Pelvic fracture	7	Pelvic fracture	6
Spine fracture	3	Long bone fracture	5
Facial fracture	3	Spine fracture	1
Chest		Chest	
Hemo/pneumothorax	18	Hemo/pneumothorax	4
Flail chest	2	Traumatic rupture aorta	1
Traumatic rupture aorta	1		
Head			
Closed head injury	8		

* 2.7 associated injuries per patient.
† 6.2 associated injuries per patient.

TABLE 7. *Comparison of Survivors* vs. *Patients who Exsanguinated and Patients who Died of Other Causes*

	Survivors	Patients who Exsanguinated	Death of Other Causes
No.	22	9	8
Age	31.8 ± 15.3	45.3 ± 18.4	26.6 ± 6.8
ISS	34.7 ± 10.6	36.2 ± 5.8	47.7 ± 5.9*
Grade liver injury	4.13 ± 0.70	3.7 ± 1.0	3.5 ± 0.5
Transfusion	12.4 ± 8.0	17.9 ± 7.4	25.8 ± 24.8
Lowest temperature	34.4 ± 1.6	31.6 ± 1.2*	33.4 ± 1.9
Lowest pH	7.24 ± 0.10	7.12 ± 0.11†	7.16 ± 0.12
PT	13.9 ± 1.35	43.2 ± 40‡	27.7 ± 29.8
PTT	32.5 ± 6.67	109 ± 70.4†	64.7 ± 61.8

* $p < .001$.
† $p < .01$.
‡ $p < .05$.
ISS, injury severity score; PT, prothrombin time; PTT, partial thromboplastin time.

patients, which was significantly lower than in patients with nonliver injuries. Because the groups were so comparable, we used grouped data on liver and nonliver injuries in further analysis.

Comparing data on the population broken into three groups (Table 7), we found important differences. Patients who exsanguinated were older than patients who survived or died of other causes. The patients who bled to death were 2 C colder than survivors or patients who died of other causes. These patients were also far more acidotic and coagulopathic than survivors. It should be re-emphasized that the coagulopathy was present on admission to the ER and did not reflect the development of coagulopathy intraoperatively from consumption or dilution. The five patients who bled to death in the OR were probably not salvageable by any technique, because all had preoperative cardiopulmonary resuscitation or resuscitative thoracotomy. The patients dying of other causes (head injury, multiple organ system failure associated with sepsis, myocardial infarction, and a tracheoinnominate artery fistula) were found to have a statistically higher ISS than survivors or patients who bled to death. Patients dying of other causes had very high ISS and correspondingly had higher transfusion needs (an average of 25.8 ± 24.8 units; range, 4 to 88) because most had significant preoperative coagulopathy.

We stratified the patients by risk factors of age, pH, temperature, PT, PTT, and transfusion need (Table 8). The risk of death stratified by age did not by itself have meaningful importance. The death rate of patients over the age of 50 was not significantly higher than that for patients under 50 years of age. We found statistically significant greater mortality rates in patients with pH ≤ 7.18, PT ≥ 16, or PTT ≥ 50. No significant differences in mortality rates were seen in patients with temperature ≤ 33

TABLE 6. *Comparison of Liver Injury and Other Injury*

	Liver Injury	Other Injury
No.	31	8
Age	32.0 ± 13.2	41.0 ± 23.3
ISS	37.8 ± 10.5	38.3 ± 9.3
Mortality rate	14 (45.2%)	3 (37.5%)
Transfusion	16.6 ± 15.7	15.5 ± 6.0
Lowest temperature	33.8 ± 1.8	34.1 ± 2.1
Lowest pH	7.18 ± 0.10	7.24 ± 0.17
PT	25.2 ± 28.4*	14.3 ± 1.4
PTT	56.4 ± 57.3	50.5 ± 28.6

* $p < 0.05$.
ISS, injury severity score; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 8. *Mortality* vs. *Risk Factors*

Mortality	Risk Factor	Mortality
42%	<50 Age ≥50	50%
67%	≤7.18 pH >7.18	26%*
55%	≤33° Temperature <33 C	20%
29%	<16 PT ≥16	78%*
29%	<50 PTT ≥50	100%*
20%	<10 Transfusion ≥10	59%

$p < 0.05$.
PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 9. *Regression Analysis*

PT *vs.* PTT	4 = 0.938
Temperature *vs.* pH	r = 0.511
Temperature *vs.* PTT	r = −0.497
Temperature *vs.* PT	r = −0.233
Temperature *vs.* transfusion	r = −0.158
pH *vs.* transfusion	r = −0.334

PT, prothrombin time; PTT, partial thromboplastin time.

C compared with patients with temperature > 33 C, although the trend was much worse and the risk of death was high in the hypothermic group. Transfusion of 10 or more units of blood carried a high mortality rate (59%), but it did not achieve statistical significance compared with less than 10 units' transfusion. These points of division: pH ≤ 7.18, temperature ≤ 33 C, PT ≥ 16, PTT ≥ 50, and transfusion ≥ 10 units of blood were looked at as grouped risk factors. We found that patients with four to five risk factors positive (n = 3) had 100% mortality rate, those with two to three risk factors positive (n = 12) had a mortality rate of 83%, and patients with zero to one risk factors positive (n = 24) had an 18% mortality rate. The risk of dying with four to five risk factors positive was significantly higher than with zero to one ($p < 0.04$), as was the risk of dying with two to three risk factors positive ($p < 0.003$).

Multiple regression analyses of the data were done to find significant correlations in trends (Table 9). The strongest correlation (r = 0.938) was in examining coagulopathy, and an obvious correlation existed between measures of coagulopathy—the PT and the PTT—showing that when one measure of coagulation became abnormal the other would also be similarly abnormal. We believed that decreasing temperature would correlate well with the development of acidosis (Fig. 1), but found only a moderately strong correlation (r = 0.511). Strong efforts at maintaining proper temperature of the massively transfused patient were visible in examining the correlation of temperature and transfusion needs. Despite massive transfusion with expected decreased body temperatures, there was only a weak correlation found (r = −0.158, Fig. 2).

Postoperative complications were common in patients initially surviving the operation. Septic complications developed in six survivors (27%). There were 5 abdominal abscesses (23%), 2 wound dehiscences, and 2 enterocutaneous fistulas. We suspected that packing patients who sustained hollow visceral injuries with more contaminated operations would be followed by a higher incidence of infectious complications than in patients with only solid visceral injuries, but found the opposite. Patients sustaining hollow visceral injuries had a 14% incidence (1/7) of

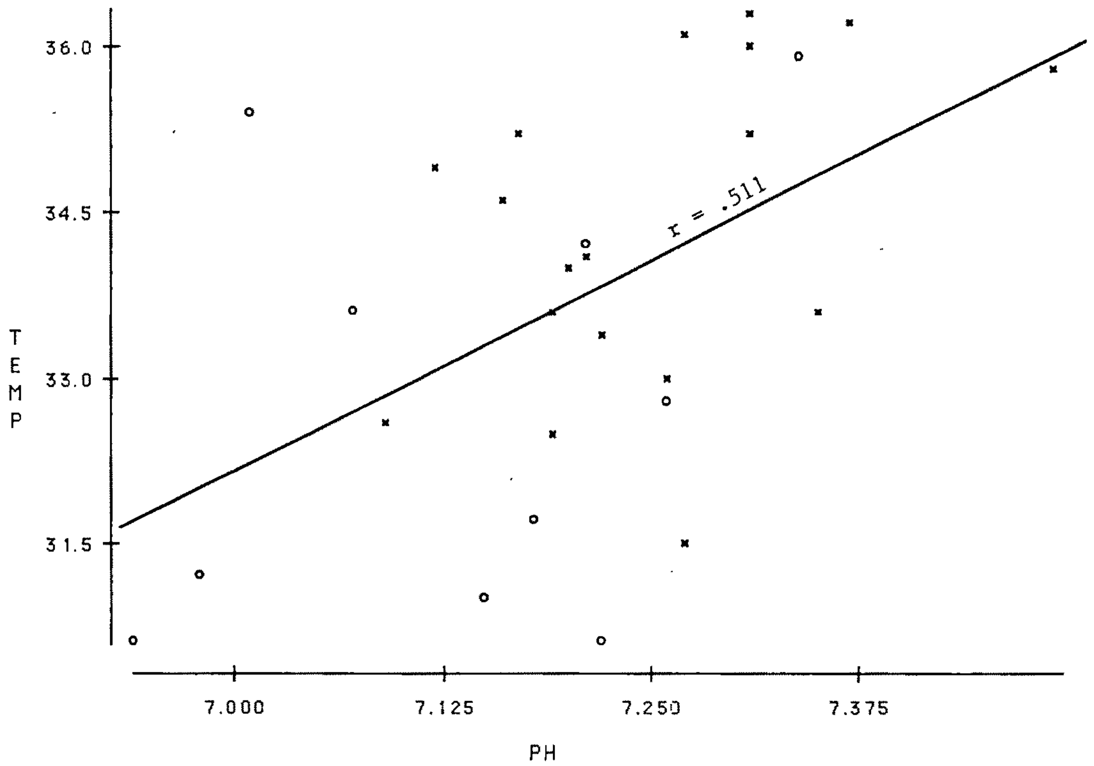

FIG. 1. Correlation of temperature (C) vs. pH. Circles represent nonsurvivors; x represents survivors.

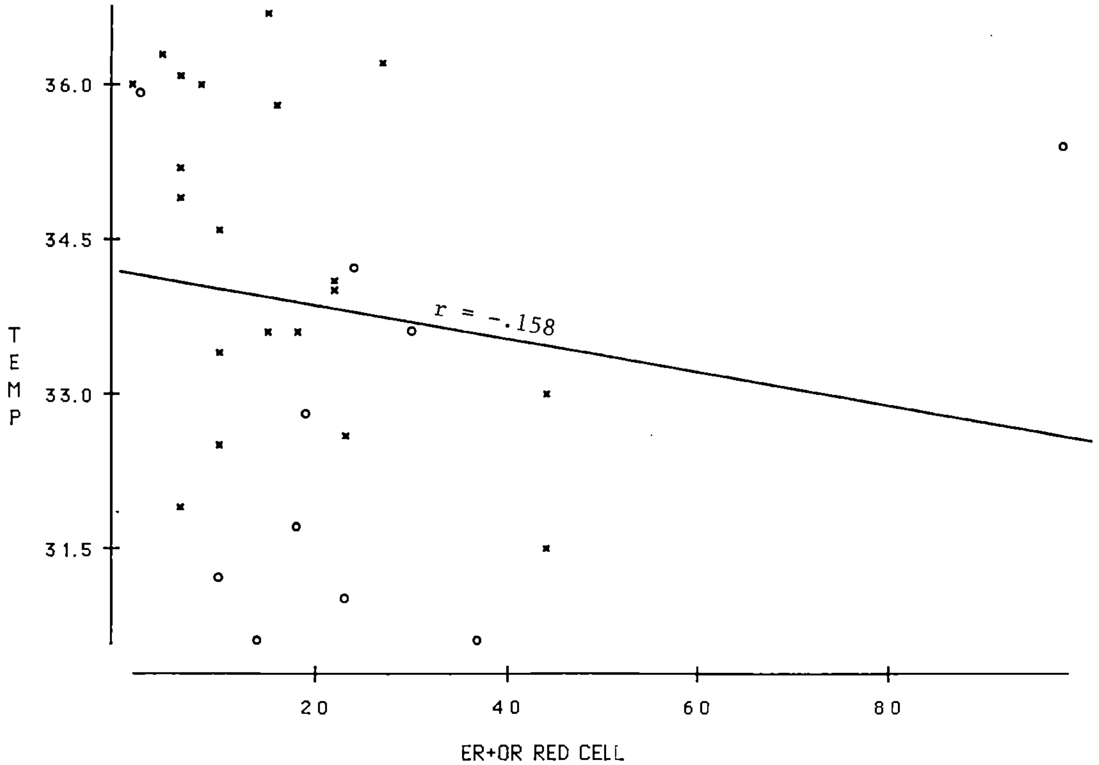

FIG. 2. Weak correlation of temperature decreasing with increasing transfusion. Circles represent nonsurvivors; x represents survivors.

abdominal abscess, whereas 27% (4/15) of the patients with solid visceral injuries only developed septic complications. We suspected a larger duration of packing in patients developing complications, but found that those patients developing septic complications had packs removed 2.2 ± 0.4 days (range, 2 to 3 days) after injury, no different from those not developing complications: 2.0 ± 1.0 days (range, 1 to 7).

Discussion

Packing of the abdomen for hemorrhage has undergone a rebirth since being soundly discouraged after military experience in World War II and the Vietnam War. Packing of liver injuries was repopularized by preliminary reports in the 1980s by Feliciano et al.,[4] Svoboda et al.,[5] and Carmona et al.[6] These authors used perihepatic packing as an adjunct in obtaining hemostasis in coagulopathic patients sustaining major liver injuries. Survival was found to be good (83% to 90%) in patients believed otherwise to be unsalvageable.

The technique of the use of packing has improved from the packs used decades before. No longer are packs placed in the manner of vaginal packing to be withdrawn through holes in the abdominal wall. Delayed hemorrhage and poor control of hemorrhage are the problems with loose packs of rolls of gauze. Modern techniques employed are dry laparotomy pads placed directly over the injury with the abdomen closed under tension to provide tamponade to a bleeding wound. Packs are carefully removed at a planned second laparotomy once the patient has stabilized hemodynamically, become normothermic, and appropriate correction of coagulopathy has occurred. Loose packs of gauze and Penrose drain packs were not found to be effective.[7] Planned re-exploration has been suggested as early relaparotomy—12–24 hours[5]—or as a delayed relaparotomy at 5 days.[4] The concern that removal of the packs would cause reactionary hemorrhage as the clot was dislodged from the liver surface led to the use of plastic-covered laparotomy pads by Feliciano et al.[1] The ability to close the abdomen rapidly and under tension may be very difficult in patients with packs and massive edema of the bowel. Towel clip closure of the abdomen may aid and speed such closure compared with retention suture techniques or plastic silo techniques. Closure of the abdomen tightly after placement of multiple laparotomy pads directly on the wound has the potential side effect of causing undesirable rises in intra-abdominal pressure after operation. Mesh closure of the abdomen has been used in abdomens that could not otherwise be closed without compromising bowel viability or ventilation. Cue et al.[3] found a decreased intra-abdominal abscess rate after mesh closures of the abdomen, and recommends mesh to aid closure in patients with massive edema, packs, and tenuous pulmonary status.

The complications of packing are thought to be an increase in septic complications after pack removal. The occurrence of intra-abdominal abscesses (23% of our survivors, 18% in other series[1]) seems quite high and is likely attributable to the unfortunate combination of operative field contamination, presence of a foreign body, and immunocompromise brought about by massive transfusion, shock, and multiple system injury. We did not have any patient whose abdominal packing caused such great intra-abdominal pressure that the patient could not be ventilated or that caused oliguria.

Packing has not been uniformly successful in stopping all deaths from exsanguination. The multicenter study of liver injuries[2] found a 59% survival in patients packed as an adjunct to surgical repair of severe liver injuries. Fifty-seven per cent survival was reported by Feliciano et al. in 1986[1] in a population of mostly penetrating trauma victims. Feliciano et al. importantly identify a group of patients packed in desperation who all exsanguinated regardless of efforts. These are patients operated on with prolonged profound hypotension, preoperative cardiac arrest, or emergency thoracotomy for cardiac arrest. Cue et al.[3] reported an overall mortality rate of 49% in a population of patients undergoing mostly blunt injuries, which is similar to the Vanderbilt experience with an overall mortality rate of 44%. Exsanguination occurred in 23% of the Vanderbilt experience, implying that 77% of the patients lived that might well not have survived an initial operation without packing. We found that our five deaths in the OR were patients packed in desperation who were in extremis before operation and agree that no surgical techniques currently exist that will save this group of patients.

Packing as an adjunct to the management of severe liver injuries (grades 3, 4, and 5) cannot be proven prospectively to improve survival. The multicenter liver injury study[2] found overall mortality rates for grade 3, 4, and 5 injuries to be 25%, 46%, and 80% in a group of patients surgically managed with standard techniques in which only 16% were packed. In comparison, our mortality rates for grade 3, 4, and 5 injuries of 56%, 43%, and 29% are respectable when viewed in the context that these patient were packed for unmanageable hemorrhage. Our survival rate of 62.5% for patients packed for pelvic and retroperitoneal hemorrhage seems reasonable in comparison with our liver injury patients, whose survival is 55% and whose age, ISS, transfusion need, acidosis, hypothermia, and coagulopathy is very similar.

The decision to pack is a difficult one and the timing at which packing should be done is controversial. General guidelines often recommend considering packing when blood loss in liver injury patients reaches 10 units.[1,3] Acidotic and hypothermic patients have been recommended to be packed,[4] but more specific guidelines have not been widely developed. Consideration of packing or changing surgical technique at 6 units of blood loss[8] is a thoughtful recommendation. It is easy for a surgeon to lose track of blood loss and continue futile techniques of suturing and cautery long after the patient is profoundly coagulopathic. Packing in patients with injuries to the retrohepatic vena cava and large intrahepatic veins has been thought to be contraindicated,[1] but recent experience has shown that packing may be a helpful adjunct in patients with such injuries.[3]

It is difficult to separate out the most important factor in a patient who has confounding problems of acidosis, hypothermia, and coagulopathy. They are clearly interrelated and are critically important in survival.[9] It seems clear that preventing hypothermia, acidosis, and coagulopathy will be beneficial, but it is not clear that correction of these factors can be done intraoperatively with proven improvement in survival.

Standard rewarming techniques of irrigation of body cavities with warm saline solution, warming intravenous fluids and blood products, using warmers on anesthetic gases, and heating pads on the operating table fails to significantly rewarm cold patients. Gentilello et al.[10] have evaluated the correction of coagulopathy in experimental animals by rapid rewarming techniques using a heparinless extracorporeal circulatory warmer and find rapid correction of hypothermia-induced coagulopathy without need for plasma or platelets. Human application of this technique remains to be shown effective, but this technique certainly seems promising.

Our current recommendations for management of the patient with uncorrectable bleeding is to use packing when sutures no longer suffice. We recommend standard surgical techniques in liver injuries, using manual compression of the liver, generous mobilization, prolonged inflow occlusion using the Pringle maneuver, hepatotomy, and selective vascular ligation techniques as outlined by Pachter et al.[11] We have had success in repair and ligation of hepatic venous injuries using this technique without the use of an atriocaval shunt. To forestall the development of coagulopathy in patients arriving in the operating room normothermic, nonacidotic, and noncoagulopathic, we consider packing of the abdomen for either liver or nonliver injuries when blood transfusion requirements exceed 10 units of blood. If patients intraoperatively drop their temperature below 33 C, their pH below 7.18, or show signs of coagulopathy, we consider packing at that point. In patients arriving at the operating room cold, acidotic, and coagulopathic, we consider packing long before 10 units of blood are administered. We do not plan relaparotomy for pack removal until hypothermia, acidosis, and coagulopathy have been corrected, which frequently takes 48 to 72 hours. Patients who continue to bleed after packing must be re-explored if survival is to be expected.

Acknowledgments

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DISCUSSION

DR. H. LEON PACHTER (New York, New York): Dr. Bland, Dr. Jones, Members and Guests, I want to thank Dr. Sharp and the Vanderbilt group for allowing me to review their manuscript. And, as Dr. Sharp has noted, packing got a bad reputation in the early part of World War II, when the results were disastrous. In fact, I have heard from some people that it was a court martial offense to pack [a liver injury] after 1943. Perihepatic packing has been resurrected into the realm of acceptability, however, and as Dr. Sharp has outlined, it has really become a technique that is the procedure of choice when faced with the threat of exsanguination from a coagulopathy. Detailed and specific guidelines for packing have been lacking, and the institution of this technique has for the most part been brought about by an all-inclusive term such as nonmechanical bleeding or coagulopathy. To the credit of the Vanderbilt group, some science has finally been introduced into this very important concept, because they have identified specific objective risk factors by which a handle can be placed on the use of packing, which can be monitored easily in all operating rooms. Additionally, Dr. Sharp and the Vanderbilt group have shown us that associated hollow viscus injuries are not a contraindication to packing, and in fact, as you just saw, the abscess rate was no different in those patients that had hollow viscus injury and those that did not. Dr. Sharp and the Vanderbilt group are really modest when they report a mortality rate of 44%, 17 of 39 patients. If you exclude the three patients that had head injuries and the five patients that died in the operating room when packing was used as a last desperate maneuver, their adjusted mortality rate was only 23%.

As you can see, in the data here from the last 8 years, there are about 250 patients available for analysis. One hundred sixty-three survived, which is a rate of 65%. And it is quite clear to me that most of those patients would have died had any other technique been used. But packing, however, despite the results just cited, is not to be equated with motherhood and apple pie. Twenty-three per cent of the patients in this series exsanguinated despite the use of packing. And when packing is used as a last desperate maneuver, the results are predictable.

As we see here, when used as a last desperate maneuver in the patients treated by Drs. Feliciano, Cogbill, and Cue (n = 47), only one survived when packing was used as a last desperate maneuver. When used as an adjunctive maneuver, however, of 106 patients, 71 patients survived (67%). I have a few questions for the authors.

The first is, what percentage of your patients with complex hepatic injuries do you pack? In other words, how often should packing be used? The second is, what are the authors feeling on monitoring intra-abdominal pressure to prevent oliguria and subsequent renal failure? And what are the authors' feelings on the use of packing when confronted with a juxtahepatic venous injury, considering the reports by Richardson and Cue from the Louisville group, and Sandy Beal, where several patients with retrohepatic caval injuries were packed and subsequently salvaged at a second surgery? And, lastly, I was intrigued by the fact that there was no difference in the abscess rate whether the packs were removed early or late. Conventional wisdom has been to try to get them out as soon as possible; however, this should only be done after the coagulopathy, acidosis, and hypothermia have been corrected. I enjoyed this paper very much. And I want to thank the Association for the privilege of the floor.

DR. H. HARLAN STONE (Phoenix, Arizona): A little more than a decade ago, Drs. Feliciano, Maddox, and Jordan stressed the importance of packing liver injuries when the patient was facing exsanguination. We at Grady Hospital were influenced by their experience and accordingly began using abdominal packing to manage these types of patients.

(Slide) Our initial experience, as you will see in the pack column, was quite good, and we presented these data at this meeting 9 years ago. Subsequent experience showed no improvement over what we had done initially. Several other problems arose, and we noted that there were a number of patients in whom we never gained control of their coagulopathy despite correcting pH, warming the patient, and giving fresh frozen plasma as well as platelets. We also noted that most patients in whom we failed to control the coagulopathy had significant liver disease. They either had advanced cirrhosis, had acute hepatitis, or in one patient, we had left a large piece of ischemic liver within the abdomen. As a result, this patient was producing large amounts of fibrinolysin. So my question here is, what was the incidence of liver disease in those patients on whom you did not get a handle, and how many of these patients did have an ischemic segment?

Secondly, we noted that certain problems were created by our packing. We preferred operating room gowns stuffed in the pelvis, with the arms of those gowns up the gutter. But with this increased intraabdominal pressure to stem the tide, that is, to tamponade, we observed the diaphragms to be elevated, and mechanical ventilatory problems ensued. PEEP was thus required, and correspondingly fluid therapy in these patients necessitated monitoring by pulmonary artery pressures to offset an impaired venous return to the heart. Often these patients would also develop renal failure. Richards, Scoville, and Shin described this particular complication about 6 or 8 years ago and incriminated the significantly elevated caval pressures being transmitted to the renal veins. Such often forced an earlier pack change because the patient had become anuric. As queried by Dr. Pachter, I wonder what was the incidence of renal failure in your patients? When you did remove the packs, did the patients regain good renal function, or did these patients progress and have infarcted kidneys?

Finally, I want to congratulate you on a good piece of work. I am glad that this recourse is once again being stressed, for indeed packing can be lifesaving. Thank you.

DR. GEORGE M. WATKINS (Peoria, Illinois): Drs. Bland, Jones, and Audience, I too thought this was an excellent paper. And my conclusions would be the same as those reached by the authors and Dr. Pachter. I would pack earlier. Packing early has got one problem attendant. When starting packing earlier, inevitably one begins to miss some vascular injuries. Then one is faced with a patient who is either still bleeding or not bleeding. You either have to wait them out or reoperate on them and sometimes find something, sometimes find nothing, but nevertheless reoperating when you should be observing the patient, getting rid of their acidosis, the death spiral due to hypothermia, etc. The alternative is to wait them out and hope. An in-between method is of course to do either angiography or venography in the operating room or someplace else while keeping this very important warmth function present. I would like to ask the authors, do they consider angiography in these situations? Will they be doing it more, because they are packing earlier? And if so, will they get rid of the radio-opaque material as alluded to by Dr. Stone so that the x-rays can be a little better?

As far as the renal function, I was going to ask the same question in a different manner. A little bit of pressure does alter the outer renal cortical flow, not causing renal failure, but actually impairing renal function.

And did you happen to look at any of these patients, or the whole group, to see if renal function of those that when you took packs out at the end of the operation improved. Did renal function improve in the operating room as measured by either volume, specific gravity, or creatinine clearance. Thank you for the privilege of the floor.

DR. KENNETH W. SHARP (Closing discussion): I would like to thank the discussants for the kind questions. They were not nearly as critical as I expected. Dr. Pachter, you asked about the incidence of the need for this technique. We currently pack fewer than 10% of our patients with severe liver injuries. We have believed that to pack more than that may be excessive, to pack less may result in losing patients.

As far as monitoring of intra-abdominal pressure, as far as using manometers hooked to the Foley catheter balloon and other techniques that have been described, we have not routinely performed such measures. In this series, one patient was reopened in the surgical intensive care unit when she became impossible to ventilate and anuric. No other patient became overtly anuric or oliguric in this series. As far as the use of packing with juxtahepatic venous injuries, we have used it in two cases in this series. There were two patients who were coagulopathic and who had initial debridement. Juxtahepatic, hepatic vein injuries were suspected, the patient was packed, and a relaparotomy ligation of those hepatic veins was performed. So two of 30 liver patients would be approximately an 8% incidence. Dr. Stone, I appreciate your question about the incidence of coexistent liver diseases. When I was a resident at Hopkins, you visited, and as you came around, I had just pronounced a patient dead who had fractured his cirrhotic liver in half when a pickup truck fell on him.

None of the patients in this series were identified as having pre-existent cirrhosis, hepatitis, or other liver diseases that we knew of. None were recorded in the operative notes or were known to the operating surgeons. As far as ischemic liver that was left behind at the time of packing, this was indeed frequent. I cannot quantify how many patients had how much ischemic liver that went on and contributed to their further death. But there were the patients who survived two relaparotomies and unpacking, and had their livers debrided of all obviously necrotic liver. The complications of packing, such as difficulty in ventilation and anuria, were uncommon, and as I mentioned, only occurred in one patient that we identified.

Dr. Watkins, the question about adjunctive angiography in the patient who continues to bleed after packing of the abdomen is *au courant.* I think that several authors have reported good results with postoperative angiography in these bleeding patients. We have not been comfortable in taking a bleeding patient to the angiography suite. That's been a very lethal trip. We have not done angiography in these patients, preferring to either re-explore them or assume that they were unsalvageable and let them die. I cannot answer the question about any sign of subtle renal improvement that occurred in these patients when they were unpacked. We did not record these variables. Thank you for the privilege of the podium.

Abbreviated Laparotomy and Planned Reoperation for Critically Injured Patients

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The triad of hypothermia, acidosis, and coagulopathy in critically injured patients is a vicious cycle that, if uninterrupted, is rapidly fatal. During the past 7.5 years, 200 patients were treated with unorthodox techniques to abruptly terminate the laparotomy and break the cycle. One hundred seventy patients (85%) suffered penetrating injuries and 30 (15%) were victims of blunt trauma. The mean Revised Trauma Score, Injury Severity Score, and Trauma Index Severity Score age combination index predicted survival were 5.06%, 33.2%, and 57%, respectively. Resuscitative thoracotomies were performed in 60 (30%) patients. After major sources of hemorrhage were controlled, the following clinical and laboratory mean values were observed: red cell transfusions—22 units, core temperature—32.1 C, and pH—7.09. Techniques to abbreviate the operation included the ligation of enteric injuries in 34 patients, retained vascular clamps in 13, temporary intravascular shunts in four, packing of diffusely bleeding surfaces in 171, and the use of multiple towel clips to close only the skin of the abdominal wall in 178. Patients then were transported to the surgical intensive care unit for vigorous correction of metabolic derangements and coagulopathies. Ninety-eight patients (49%) survived to undergo planned reoperation (mean delay 48.1 hours), and 66 of 98 (67%) survived to leave the hospital. With the exception of intravascular shunts, there were survivors who were treated by each of the unorthodox techniques. Of 102 patients who died before reoperation 68 (67%) did so within 2 hours of the initial procedure. Logistic regression showed that red cell transfusion rate and pH may be helpful in determining when to consider abbreviated laparotomy. The authors conclude that patients with hypothermia, acidosis, and coagulopathy are at high risk for imminent death, and that prompt termination of laparotomy with the use of the above techniques is a rational approach to an apparently hopeless situation.

CRITICALLY INJURED PATIENTS, such as those suffering from grade V liver injuries or multiple abdominal vascular injuries, may lose blood at the rate of 20 to 40 units per hour while attempts are made to control the hemorrhage. Although anesthesiologists and blood banks may keep pace with this rate of hemorrhage for some time, severe metabolic consequences are inevitable.[1-3] Hypothermia from evaporative and conductive heat loss occurs in spite of warming blankets and blood warmers. The metabolic acidosis of shock is exacerbated by aortic clamping, vasopressors, massive transfusions, and impaired myocardial performance. Coagulopathy due to dilution and hypothermia complete the lethal triad. Each of the above factors reinforces both itself and the other derangements, resulting in an extremely fragile patient who is only minutes away from a fatal arrhythmia. The author's approach to such patients is to break the cycle by abruptly terminating the operation to prevent further heat loss and to transfer the patient to the intensive care unit for rewarming and correction of the coagulopathy. Implicit with this decision is that sufficient time may not be available to treat all injuries. Also, the massive edema of the bowel and retroperitoneum that inevitably occurs in this setting may preclude conventional abdominal closure because the increase in intra-abdominal pressure may cause immediate renal and respiratory failure.[4-11] The purpose of this study is to evaluate the authors' use of unorthodox abdominal closures and other temporary measures to prevent the imminent death of these critically injured patients.

From December 1983 through April 1991, 200 critically injured patients were treated at the Ben Taub General Hospital in Houston, Texas. A variety of unorthodox methods were used to abruptly terminate the initial laparotomy, with the intention of completing the procedure at a planned reoperation.

Data were obtained from patient records and supple-

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mented by information from a weekly surgical log. Complete information was available for 163 patients (82%). This rather low figure was primarily due to the frantic activity of the physicians and nurses who treated the patients. The ordering of tests and recording of observations were subordinate to the exigencies of patient care. Percentages were based on available data and are specified where necessary. Patients with incomplete data were excluded from statistical calculations.

There were 183 (92%) men and 17 (8%) women, who ranged in age from 15 to 77 years, with a mean of 31 years. Penetrating trauma was the cause of 170 (85%) injuries, and blunt trauma was responsible for the remaining 30 (15%). The Revised Trauma Score, Injury Severity Score, and Trauma Index Severity Score age combination index (TRISS) predicted survival for patients with penetrating injuries were 5.0%, 32%, and 57%, respectively (median, 6.4%, 26%, and 76%). For blunt trauma, the mean Revised Trauma Score, Injury Severity Score, and TRISS were 5.4%, 41%, and 60%, respectively (median, 6.4%, 41%, and 69%).

Emergency center resuscitation generally followed American College of Surgeons Advanced Trauma Life Support Program (ATLS) guidelines.[12] Sixty patients (30%) required resuscitative thoracotomies either in the emergency center or in the operating room (OR). The median delay from admission to operation was 25 minutes for patients with penetrating injuries and 80 minutes for patients injured by blunt trauma. Median systolic blood pressure on admission was 72 mmHg and was similar for patients with both blunt and penetrating injuries.

In the OR, all patients were explored through midline incisions. Injuries often associated with severe hemorrhage are listed in Table 1. One hundred twenty-five patients suffered major abdominal vascular injuries. In addition, 10 patients suffered major vascular injuries outside the abdominal cavity. Of 102 patients with liver injuries, 15 had juxtahepatic venous injuries (grade V), and 11 required atriocaval shunts.

Physiologic parameters, including pH, core temperature, and systolic blood pressure, were noted at the beginning and end of the initial operation. The lowest values of each were also recorded (Table 2). Intraoperative transfusion and fluid requirements are shown in Table 3. Every attempt was made to warm blood products and crystalloids solution to 37 C before administration. The rate of transfusion of red blood cells ranged from 1.3 to 42.7 U/hour during the operation. The mean rate of red cell transfusion was 11.7 U/hour (median, 10.9), and 20 patients (10%) received red cells at a rate in excess of 20 U/hour. Pharmacologic support of cardiac output was required in 126 patients (63%). Epinephrine was used most often (116 patients); the remaining 10 patients were treated with dopamine.

TABLE 2. *Mean Physiologic Parameters During the Initial Operation*

	Beginning of Operation	Lowest Recorded Value	End of Operation
Systolic blood pressure (mmHg)	102	63*	102*
Core temperature (C)	34.0	32.1	32.7
pH	7.18	7.09	7.19

* Excludes patients who died in the operating room (blood pressure = 0).

On concern of the patient's impending death, several techniques were used to terminate the operation. Laparotomy pads were used to tamponade diffusely bleeding surfaces in 171 patients (86%). The liver was packed in 74 patients (38%), the retroperitoneum in 65 (33%), and the pelvis in 32 (16%). Thirty-four patients with enteric injuries (17%) requiring resection and anastomosis or colostomy were treated by ligating or stapling the intestine on both sides of the injuries (Fig. 1).13 This was done to prevent further contamination of the peritoneal cavity. In most patients, ligation resulted in isolated intestinal segments similar to closed loop bowel obstructions.

Temporary intravascular shunts, secured with snare tourniquets, were used in four patients. All shunts were used for injuries that would have required interposition grafts or end-to-end anastomosis, but sufficient time for the repair was not available. One was used to bridge a defect between the common iliac vein and vena cava, and three were used to bridge defects in the iliac artery.

Aortic clamping was used to support circulation to vital

TABLE 1. *Selected Associated Injuries*

Vascular		Solid Organ	
Inferior vena cava	48	Liver	102
Aorta	21	Pancreas	30
Iliac	66	Kidney	41
Renal	45	Spleen	25
Major splanchnic	50	Pelvic fracture	9
Heart	7		
Other major vascular	21		

TABLE 3. *Mean Transfusion and Fluid Requirements*

	Initial Operation	24-hr Period After Initial Operation	Reoperation
Crystalloid (L)	11.6	5.9	3.3
Packed red cells (units)	22	9.8	4.1
Fresh frozen plasma (units)	4.4	8.8	1.9
Platelets (units)	6.3	10.7	4.2

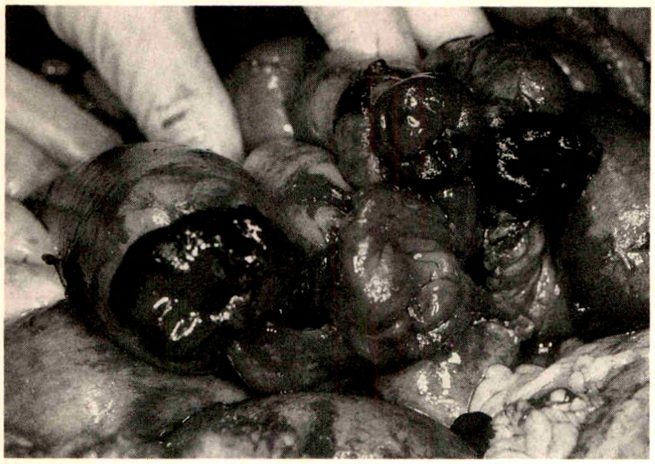

FIG. 1. Appearance of small bowel and colon at reoperation after treatment of original enteric injuries by ligation. The ligatures are still in place.

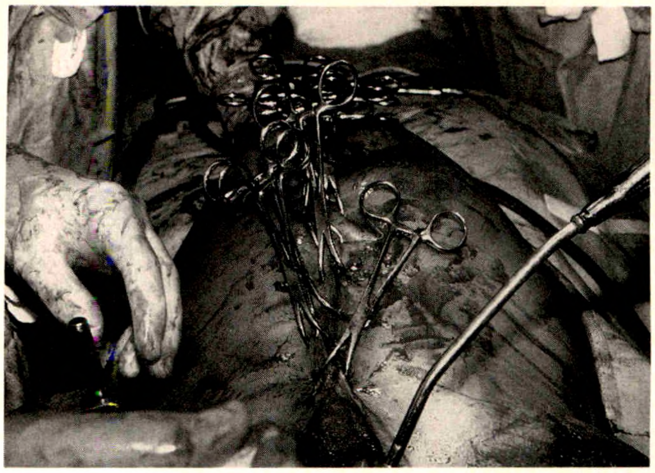

FIG. 3. Towel clip closure. Note the laparotomy pad used to pack the liver at the bottom of the incision.

organs in most patients. In 11 patients, infrarenal aortic clamps could not be removed before abdominal closure without the systolic blood pressure falling to below 50 mmHg, in spite of epinephrine or dopamine. These clamps were brought out through the abdominal incision and gradually released as the patient either improved or died (Fig. 2). Two other patients had intentionally retained vascular clamps on the iliac artery when the clamp controlled associated hemorrhage but the patient's condition precluded further attempts at definitive control.

No patient in this series had a conventional closure of the abdominal incision. The most commonly employed closure was performed with towel clips to approximate only the skin.[4] The clips were placed 1 to 2 cm apart and 1 to 2 cm from the edge of the incision (Figs. 3 and 4). Approximately 25 to 40 towel clips were required, depending on the length of the incision. Towel clip closure was often performed in 60 seconds, although occasionally up to 4 minutes were needed. The clips were covered with a sterile towel and secured with a large plastic adhesive barrier. Towel clip closure was the initial closure in 178 patients (89%). Eleven patients had just the skin of the abdomen closed using a 2 nylon suture. One patient died before abdominal closure; he was included in the series because of treatment with a temporary intravascular shunt.

In 10 patients, massive edema of the intestine and retroperitoneum prohibited approximation of even the skin. Silos were constructed of various rubber or plastic materials after the fashion of techniques used to treat gas-

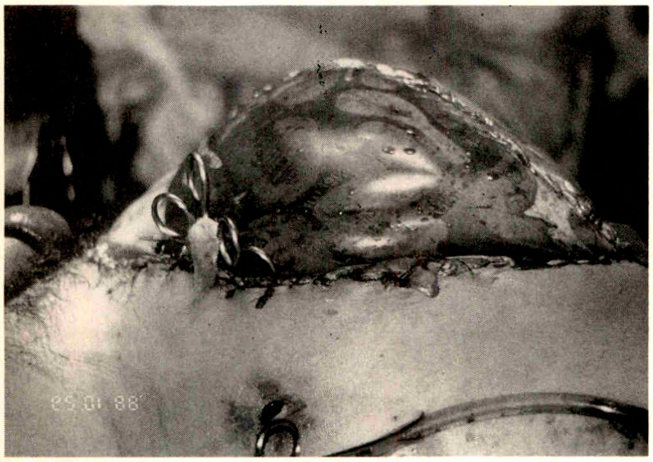

FIG. 2. Retained vascular clamps in a patient with silo closure of abdominal wound. Reprinted with permission from Feliciano DV, Burch JM. Towel clips, silos, and heroic forms of wound closure. *In* Maull KI, ed. Advances in Trauma and Critical Care. Vol. 6. Chicago: Mosby-Year Book, 1991.

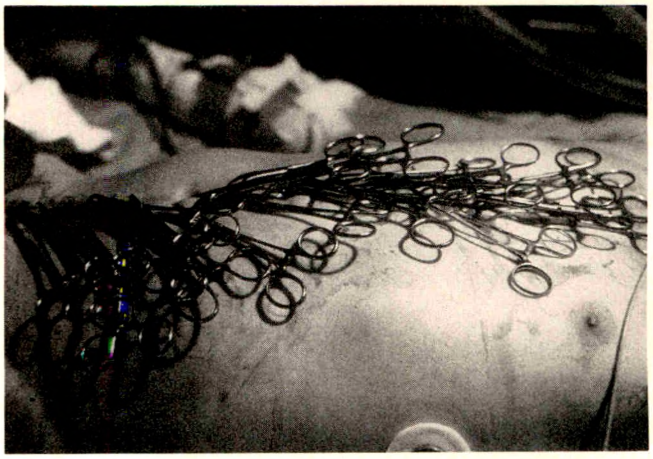

FIG. 4. Lateral view of towel clip closure. Only the skin is closed; no attempt is made to include the fascia.

troschisis and omphaloceles in neonates.[14,15] The artificial material was sutured to the skin edges with heavy monofilament suture and tailored to the shape of the incision and the bulging intestine (Fig. 5). Currently, the most popular material is a 3-L Viaflex intravenous fluid bag (Travenol Laboratories, Deerfield, IL) that has been unfolded by cutting the seam and then sterilized (Fig. 6). As many as three or four intravenous bags were sutured together to close large defects.

Results

Survival

Thirty patients (15%) died in the OR. An additional 72 patients (36%) died in the surgical intensive care unit (SICU) before planned reoperation. Figure 7 shows the length of survival for those who died before reoperation. Sixty-eight of 102 patients (67%) died within 2 hours of the end of the initial procedure. For those who reached the SICU alive, vigorous efforts were made to rewarm the patients, correct existing coagulopathies, and optimize oxygen delivery.

Rewarming was accomplished by placing the patients on heating pads (39 C) and covering them with warmed blankets. The return of core temperature to normal required 2 to 8 hours, depending on the degree of hypothermia.

Clotting factors, red cells, and crystalloids administered during the first 24 hours in the SICU (or before reoperation or death if less than 24 hours) are shown in Table 3. In general, more fresh frozen plasma and platelets were given in the SICU than during the initial operation. In contrast, crystalloid infusions were intentionally minimized to prevent further edema of the bowel and associated increases in intra-abdominal pressure.

Although all patients had clinically apparent coagulopathies by the end of the initial operation, the results of coagulation studies were seldom available in the operating room. Coagulation studies drawn at the end of the operation or on arrival in the SICU were available for 107 of 144 patients who survived for more than 1 hour in the SICU. The mean prothrombin time was 25.1 seconds (median, 17.5 seconds); the mean partial thromboplastin time was 110 seconds (median, 150 seconds); and the mean platelet count was 97 × 10^3 cells per mm^3 (median 85 × 10^3 cells per mm^3). After resuscitation, coagulation studies were available for 79 patients who survived to undergo reoperation. The mean prothrombin time for this group was 15.0 seconds (median, 11.5 seconds); the mean partial thromboplastin time was 46.0 seconds (median,

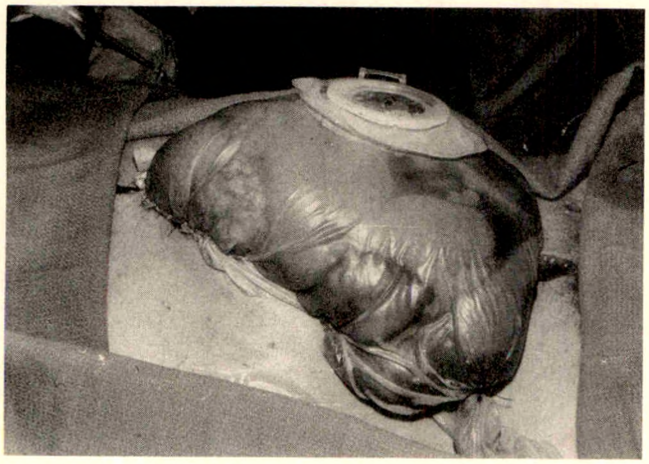

FIG. 5. Large silo constructed of a lightweight waterproof plastic barrier. Note the massive edema of the small bowel. View 24 hr postoperatively, after much of the edema had subsided. Reprinted with permission from Feliciano DV, Burch JM. Towel clips, silos, and heroic forms of wound closure. *In* Maull KI, ed. Advances in Trauma and Critical Care. Vol. 6. Chicago: Mosby-Year Book, 1991.

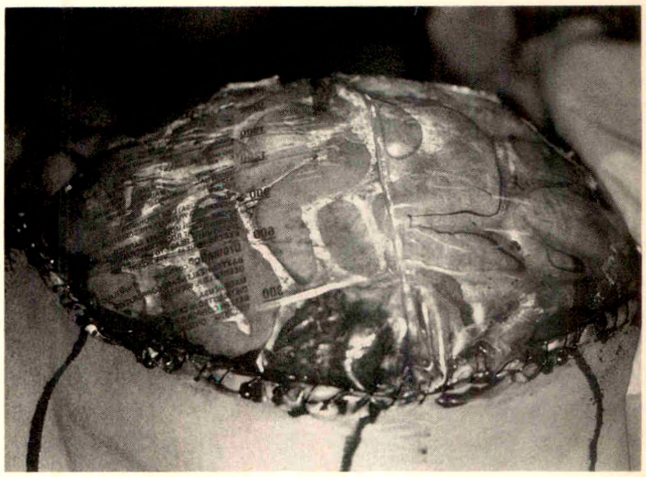

FIG. 6. This silo was constructed from a 3-L urologic irrigation bag, currently the most popular material.

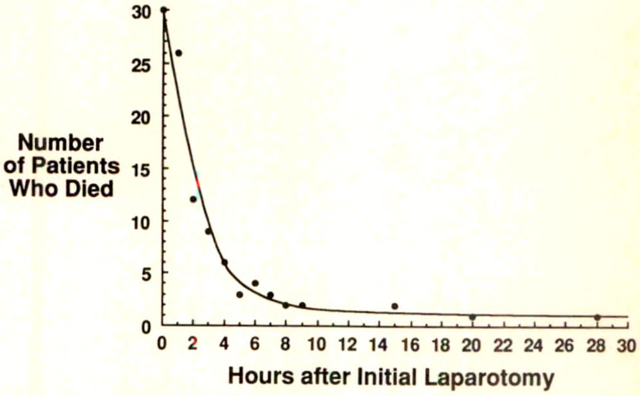

FIG. 7. Length of survival for patients who died before reoperation. Note the large number of patients who die soon after abdominal closure. One patient not included on the figure died 40 hr postoperatively.

35.7 seconds); and the mean platelet count was 120 × 10^3 cells per mm^3 (median 102 × 10^3 cells per mm^3).

Dopamine or epinephrine infusions were required to support cardiac output in 81 of 170 patients (48%) who reached the SICU alive. This figure is deceptively low because recording this information was a low nursing priority for patients who died soon after admission. For those who survived to undergo reoperation, dopamine or epinephrine infusions were required in 34 of 98 patients (35%).

Of 98 patients who underwent reoperation, 17 (17%) were operated on because of uncontrolled hemorrhage. The mean time between the end of the initial operation and reoperation was 8.7 hours (median, 10.0 hours; range, 8 to 24 hours) for this group, and only four (24%) survived to leave the hospital. For the remaining 81 patients who underwent planned reoperation, the mean time between procedures was 48.1 hours (median, 48.0; range, 3 to 208), and 62 of 81 patients (77%) survived. The survival rate for all patients undergoing reoperation was 67% (66/98), and for all patients in the series, 33% (66/200). The most common cause of death was exsanguination, which occurred in 110 patients (82%), followed by multiple organ failure in 21 (16%). The causes of death for three remaining patients were adult respiratory distress syndrome, a penetrating head injury, and a pulmonary embolism.

Survival for each technique used to terminate the initial operation is shown in Table 4. With the exception of intravascular shunts, patients survived when treated with each technique. Atriocaval shunts were not considered as adjuncts to terminate the operation. Parenthetically, five of 11 patients (45%) treated with atriocaval shunts survived.

Complications

Eighty-six patients either survived to leave the hospital or lived long enough (>48 hours) to manifest complications. Table 5 lists the significant abdominal complications. Abscesses and enteric fistulas were encountered more often (12% and 8%, respectively) than is usually seen in series of injured patients. Both patients with necrosis of the colon and one of the two with stomal necrosis required epinephrine or dopamine, which may have been a contributing factor.

TABLE 4. *Survival According to Technique*

Technique	No. of Patients	Survivors
		No. (%)
TCC	178	53 (30)
Nylon	11	8 (73)
Silo	10	5 (50)
Bowel ligation	34	7 (21)
Temporary shunt	4	0 (0)
Retained clamp	13	1 (7.7)
Packed	171	57 (33)

TCC, towel clip closure.

TABLE 5. *Abdominal Complications (*N = *86 [66])**

Complication	No. of Patients
Abscess	10 (8)
Fistula	7 (5)
Peritonitis	1 (1)
Small bowel obstruction	3 (3)
Colonic necrosis	2 (1)
Stomal necrosis	2 (1)
Pseudocyst	1 (1)
Urinoma	1 (1)

* Numbers in parentheses indicate survivors.

Patients with organ failure, septic syndrome, and other infections are shown in Table 6. All patients with multiple organ failure had respiratory and renal failure, and many in this category also had hepatic, cardiac, or hematologic failure. The term septic syndrome is used to describe patients with the clinical signs of sepsis (fever, hypotension, diaphoresis, elevated white blood cell count, and decreased systemic vascular resistance) but who do not have an apparent focus of infection. Survival for these patients was particularly poor (one of nine, 11%).

There were 13 serious wound complications, including dehiscence or evisceration in 6 patients, necrotizing infections in 4, large hernias in 2, and necrosis of the skin and subcutaneous tissue in 1. All patients but three were initially treated with towel clip closure. Two were treated with silos, which disrupted and resulted in evisceration. The remaining patient suffered a wound infection; his abdomen was originally closed with heavy nylon suture.

Six patients had serious vascular complications. Two required above-knee amputations; both had intentionally retained vascular clamps, one on the aorta and the other

TABLE 6. *Organ Failure, Septic Syndrome, and Infectious Complications (*N = *86 [66])**

Complication	No. of Patients
MOF	25 (3)
ARDS	8 (7)
ARF	2 (2)
Septic syndrome	9 (1)
Pneumonia	10 (7)
Empyema	3 (3)
Catheter sepsis	2 (1)
Urinary tract infection	1 (1)

* Numbers in parentheses indicate survivors.

MOF, multiple organ failure; ARDS, adult respiratory distress syndrome; ARF, acute renal failure.

on the iliac artery. Two patients had thrombosis of the common iliac artery; one had a temporary shunt placed in the vena cava, which thrombosed. The resultant increase in venous pressure appeared to compromise an iliac artery anastomosis. The other had ligation of the vena cava, which was followed by arterial thrombosis. Two of these patients also developed compartment syndromes, one with the retained aortic clamp and the other with ligated vena cava. One patient developed gangrene of the toes related to a high-dose epinephrine infusion that was started in the OR and continued in the SICU. One patient who died of a pulmonary embolus was treated with a retained aortic clamp. He was recovering without serious complications, but as he began to ambulate on the 9th postoperative day, the embolus occurred.

Discussion

The concept of planned reoperation for trauma patients is not new. Authors from this institution as well as others have recognized the wisdom of packing a diffusely bleeding liver, retroperitoneum, or pelvis and returning at a later date.[5,16,17] The unusual aspect of this series was the surgeon's recognition of the patient's imminent death and instituting measures to terminate the procedure as fast as possible. That the authors were able to predict which patients would die is supported by Figure 7. Of 102 patients who died before reoperation, 56 (55%) died within 1 hour of abdominal closure, and 68 (67%) died within 2 hours.

There are several indicators available to the operating team that may be helpful in predicting impending death. These include cardiac rhythm, red cell transfusions, blood pressure, core temperature, pH, coagulopathy, and various injury severity scoring systems. Ventricular arrhythmias occur in virtually all patients who die in the OR or shortly thereafter. They are characterized by wide QRS complexes, ectopy, bradycardia, and electromechanical dissociation. These arrhythmias are often refractory to antiarrhythmic drugs and cardioversion. In this series, only two of 67 (3.0%) patients who suffered a cardiac arrest in the OR were successfully resuscitated. Although ventricular arrhythmias are excellent predictors of imminent death, it is usually too late to intervene. The presence of coagulopathy is a subjective observation and does not predict imminent death. Although objective, the injury severity indices are only predictive of eventual death.

To evaluate the surgeon's ability to predict impending death, a regression analysis of available intraoperative information was performed. Death within 2 hours of abdominal closure was selected as an end point. The two factors that emerged as independent and most predictive were the rate of red cell transfusion (units per hour) and pH ($p < 0.0001$). Figure 8 is a scatter plot of pH, the rate of red cell transfusion, and 48-hour survival for 163 patients with complete data. The diagonal discriminant line was derived by logistic regression and has the following equation: transfusion rate = 35.7(pH) − 242. Patients to the left and above the line are considered at high risk for imminent death, those to the right and below, low risk. The accuracy of this discriminant (risk of death within 48 hours = 0.57, 77% correct identifications) must be tested in a prospective study to be proven. In lieu of such a study, it seems reasonable to consider abbreviated laparotomy when a patient's transfusion rate and pH approach the discriminant.

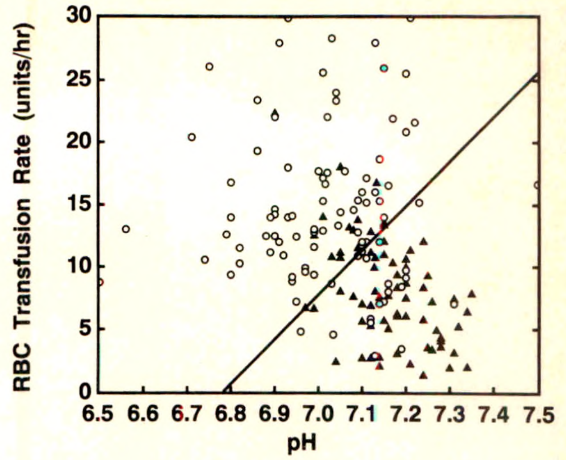

FIG. 8. Scatter plot of pH and red cell transfusion rate. Triangles represent survival greater than 48 hr. Circles represent death within 48 hr. Patients plotted above the diagonal discriminant line are at high risk for death within 48 hr of initial operation. See text.

Although the triad of hypothermia, acidosis, and coagulopathy has been recognized as a lethal combination, greater emphasis has been placed on the individual elements.[18–21] In a recent review of hypothermia and coagulopathies, Patt et al.[22] noted three mechanisms by which hypothermia interfered with hemostasis: the inhibition of the temperature-dependent enzyme-activated coagulation cascades, increased fibrinolytic activity, and reversible platelet dysfunction. Hypothermia also has profound effects on the heart and circulation, which result in hypotension, bradycardia, ventricular irritability, and metabolic acidosis.[23] It is not surprising that hypothermia has been well established as an accurate predictor of death in trauma patients.[24–26]

Attempts to combat hypothermia in trauma patients have centered around devices to warm blood and fluids for rapid administration.[1,26,27] Although these machines may be capable of transfusion rates of 1.6 L/minute, the logistics of preparing the machine at a moment's notice, procuring the blood, and running the device are formidable. Even if isothermic infusions are maintained, radiant, conductive, and evaporative heat loss in the cold, dry OR environment go unchecked. The authors believe that eliminating these sources of heat loss by closing the abdominal incision and covering the patient with warmed dry blankets is a practical if not critical adjunct.

In addition to hypothermia, other causes of coagulopathy in this setting include dilution and consumption.[1,3,28] All patients in the present series received red cell transfusions in the form of packed red cells that contain virtually no clotting factors or platelets. Only the residual plasma proteins in the patient's circulation and those produced by the liver during the operation can contribute to coagulation. Transfusion of two or more blood volumes of saline and packed red cells has been shown to decrease the level of several clotting factors to 15% of normal.[3] Platelets are lost by disseminated intravascular coagulation in addition to dilution.[1,3,28]

Most authors recommend that the use of fresh frozen plasma and platelets be based on coagulation studies and platelet counts.[1,3] Unfortunately, during the time the studies are performed, another 5 to 10 L of blood may be lost during the operation, and the patient's coagulation profile will bear little resemblance to that which was present when the tests were drawn. It is therefore necessary to replace clotting factors empirically.

Metabolic acidosis affects both the circulatory system and coagulation. Acidosis has been shown to decrease myocardial contractility and cardiac output.[29,30] Although it is known that acidosis decreases coagulation time, there is evidence that it may also trigger diffuse intravascular coagulation and cause a consumptive coagulopathy.[31] The importance of metabolic acidosis has been recognized in other clinical studies, but documentation has been scarce.[20,32] In the present study, acidosis was more predictive of impending death than hypothermia.

In addition to the above metabolic problems, the surgeons must also address the technical problem of closing the abdomen. The edema that occurs in the intestine and retroperitoneum is due to an increase in interstitial fluid and may be related to low colloid osmotic pressure.[33] This edema may be so great that abdominal closure is impossible (Fig. 5). In less dramatic circumstances, closure of even the skin may produce intra-abdominal pressures of 50 mmHg or more, as occurred in several patients in this series.

In laboratory models, intra-abdominal pressure of 30 to 40 mmHg has been shown to decrease cardiac output, redistribute blood flow from the abdomen to the thorax, cause ventilation/perfusion mismatches in the lungs, and impair renal function.[6–8,34] Clinical studies have emphasized increased intra-abdominal pressure as a cause of acute renal failure.[9–11] The cause of renal failure is not certain, but is probably related to compression of the kidney or renal veins. Decompression usually leads to a prompt return of renal function.[9–11]

Richardson and Trinkle[6] observed that increased intra-abdominal pressure in dogs caused an increase in end inspiratory pressure, a redistribution of blood flow in the lungs, ventilation/perfusion mismatches, and hypoxia. Three patients in this series had peak inspiratory pressures in excess of 80 cmH$_2$O after towel clip closure. None could be effectively ventilated, and all required removal of towel clips and the construction of silos. Apprahamian et al.[5] recently reported the utility of silos to prevent lethal increases in IAP.

In conclusion, the triad of hypothermia, coagulopathy, and acidosis is a vicious circle that heralds imminent death. The use of towel clip closure, silos, abdominal packs, ligation of enteric injuries, and other techniques permit the abrupt termination of the operation so that resuscitation can be accomplished. Closing the abdomen prevents further heat loss and aids in tamponade of diffuse bleeding. The use of pH and red cell transfusion rate may be helpful in determining when to abandon the initial operation. For patients who stabilize and undergo planned reoperation, the survival is remarkably good.

Acknowledgments

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DISCUSSION

DR. TIMOTHY C. FABIAN (Memphis, Tennessee): Drs. Bland and Jones, Members and Guests, I would like to congratulate the authors on application of some very innovative and novel approaches to salvage an awfully large group of catastrophically injured patients. We use some but not all of these techniques in Memphis. I think, certainly, one of the most beneficial I have observed is the rapid towel clip closure, and I recommend it to all of you in the audience. It can be very helpful and save lots of time.

I have the following series of questions. You alluded to this a couple of times, but I would like for you to expand on it a bit. With your TRISS methodology, you were supposed to have 57% survivals with penetrating trauma, and you actually only had 33%. I suspect this may be a limitation and a fault of quality assurance measures used for that analysis, but it bothers me that in the future all of us are going to be looking at such criteria for trauma center evaluation, because it is being proposed by many different groups, including the Joint Commission on the Accreditation of Hospitals and others.

In your manuscript, you reported resuscitative thoracotomy in the emergency room or operating room in 30%. Does this contribute to hypothermia? You are opening up another celomic cavity. We rarely do this, with the exception of patients with cardiac injuries, and I suspect that this does cause some problems. What is the mortality rate in those 30 patients? Your rate of transfusions was 1 U/hour to 43 in your manuscript. I would like to know the bell-shaped curve of those that were not bleeding very much. Why were they so catastrophically injured? What sort of unique circumstances were these patients?

Turning to the method of major vascular management, you had four shunts placed, one in the inferior vena cava and three in the ileac arteries. I would like to know the results of those specific procedures. No matter how coagulopathic these patients were, I suspect that they all thrombosed their shunts. And what was the outcome?

Additionally, your 11 aortic clamps and two ileac clamps that were left, what was the outcome of these? The incidence of compartment syndromes in these kinds of patients at our institution is relatively high, and we are very aggressive about putting catheters in for compartment pressure measurement after operation. What is your experience with compartment syndromes and loss of compartments and amputations in these patients?

Very importantly, an abdominal wall defect results from using silos that you create with plastic IV bags. Our experience has been that we can almost never get those bellies closed, and we end up putting split-thickness skin grafts on granulation tissue with definitive reconstruction at 8 to 12 months of large ventral hernias. How do you manage them in Houston? And you also mentioned that you do not use clotting studies for fresh frozen plasma, which I think none of us do in the operating room for these, again, seriously injured patients. What is the Houston formula for replacement of platelets and fresh frozen plasma when dealing with massive transfusions and coagulopathy? Thank you very much.

DR. R. NEAL GARRISON (Louisville, Kentucky): Vice President Bland, Secretary Jones, Members and Guests, Dr. Burch and colleagues are to be congratulated for an in-depth clinical study of a very complex problem, the operative management of a patient with severe hemorrhagic shock. There is much for the readers of this manuscript to consider and possibly adapt in their practice and care for the patients. And I recommend the manuscript to you. The real question for the recommended technique is when is the best time to implement such a strategy, to hasten the procedure, and to transfer the care to the intensive care unit setting *versus* continued attempts to control bleeding in the operating room.

I have two questions for the authors. You use only two variables in predicting outcome, the number of transfusions given to the patient and the systemic patient pH. What other variables were considered for your predicted equation? There are several that come to mind and have been used to manage the severity of injury or hemorrhage, such as the degree or length of time of blood pressure reduction or systemic oxygen utilization as measured by mixed venous oxygen saturation.

Secondly — and this is along similar lines of one of Dr. Fabian's questions — could the authors comment on the relative reluctance to use fresh frozen plasma in their resuscitative protocol? The average patient in this series received 22 red cell unit products, but only 4½ units of fresh frozen plasma. Yet coagulopathy was an apparent reason to hasten termination of the procedure by the operating surgeon. I thank the Association for the privilege of the floor.

DR. GEORGE M. WATKINS (Peoria, Illinois): Drs. Bland, Jones, Members and Guests, I suppose first in a moment of levity we may have an ad hoc HAC committee on hypothermia acidosis and coagulopathy to discuss these issues.

In non-jest, the patients, about a third of them, had their chests opened. The chest was opened either in the emergency room or the operating room. I am wondering what the authors have developed as a differing mode of therapy, if any, in the individuals who were so ill that they had their chests opened, presumably for hemorrhaging out, *versus* the other two thirds who did not have their chests opened in surgery. In other words, do you follow or have set up a treatment pattern, or are you more likely to close those earlier, or what else? Thank you.

DR. JON M. BURCH (Closing discussion): I would like to thank the discussants for their questions.

Dr. Fabian, I have thought about the issue of the problem with TRISS predicted survival, and it was distressing that the predicted survival was roughly half what it should have been. I think there are two reasons for this. The first one is being the reliance of that particular scoring system on the Glasgow Coma score, which in most patients with penetrating trauma — and those were the patients that dominated our series — is usually close to normal. I think that is one reason for this problem. And the other is that this is a selected group of patients. All the scoring systems were devised to evaluate a population of patients and not a selected subgroup. And I think this is the other reason for the failure of TRISS. Of the patients who had resuscitative thoracotomies, there were, as I recall, about five survivors. It was actually very, very low. And that does not include patients who were treated with atrial-caval shunts, nor the temporary intravascular shunts that I have mentioned before. In that group, of the 11 patients that had atrial-caval shunts, there were five survivors, for which we were delighted. Conversely, we are reluctant to open the chest on any of these patients. Indeed, it does create one more large gaping wound for additional blood loss and additional heat loss. And I really think we ought to try and avoid it if at all possible. With regard to the temporary intravascular shunts, three were used to bridge defects in the ileac artery, which would require either resection and anastomoses or an interposition graft. These were plastic or rubber carotid artery shunts. Of those three patients, each one of them had a disastrous outcome, either a compartment syndrome, an amputation, or a thrombosis of the iliac vessel. One patient had a temporary shunt placed to bridge a complicated injury involving the bifurcation of the vena cava and the junction of the two common iliac veins. I do not think even in retrospect this was a particularly good choice. That also thrombosed, caused an increase in the pressure of that leg to the point of thrombosis of that associated iliac artery. Of the 13 patients in the series that had clamps on either the aorta or the iliac vasculature, all but one died. The only survivor of that drastic maneuver was a young man who ultimately ended up with bilateral above-knee amputations. The abdominal wall defect can be very large in any of these patients. And one of the ways that we use to minimize this problem is to literally turn off the crystalloid in the intensive care unit and just administer blood and colloid, primarily colloid. As was pointed out, we were deficient in that in the operating room. And, generally speaking, over a period of somewhere between 1 and 3 days, enough of a diuresis has occurred in those patients who are going to survive to permit primary closure of the abdominal wound. There are times, however, that we get into the same situation that you mentioned: we have to wait for the wound to granulate and then place a split-thickness skin graft. That is a setup for intestinal fistula, and we try to avoid it whenever we can.

There were only five patients that actually had silos placed primarily. Another seven had silos placed after towel clip closure. Those we did not include in this series because we wanted to emphasize initial treatment. And I believe that we closed three of the five silos in the survivors, primarily.

Our ratio of red cell to plasma to platelet transfusion is supposed to be 1 unit of plasma for every 4 units of red cells. That has been standard over the years. We begin to replace platelets after 10 units of cells are given. Ten units of platelets are given at a time. That has been our usual practice, but clearly we did not always keep up with it.

Let me move to Dr. Garrison's questions. The variables that we evaluated in the operating room was all the clinical material that was rapidly and reliably available. This includes temperature, pH, blood pressure — not the duration of blood pressure, but how many times it happened to reach below a certain level. We also used the injury severity scores, the particular organs that were injured, the rate of transfusion, and so forth. There were many that were predictive. And as you would expect, temperature also was predictive of an intraoperative death. But it was not as predictive as pH was, or the rate of transfusion. I was somewhat surprised to see that, considering all the emphasis placed on hypothermia recently. I would like to thank the Association for the opportunity to present this paper. And on behalf of my wife Rita and myself, I'd like to express my sincere appreciation for the privilege of new membership.

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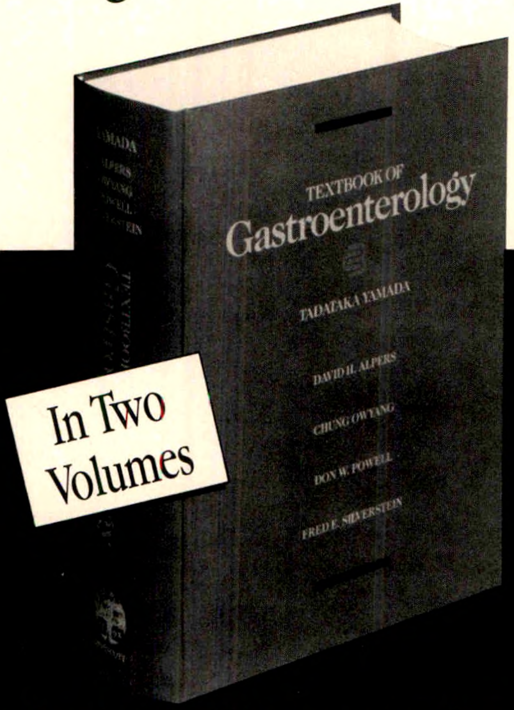

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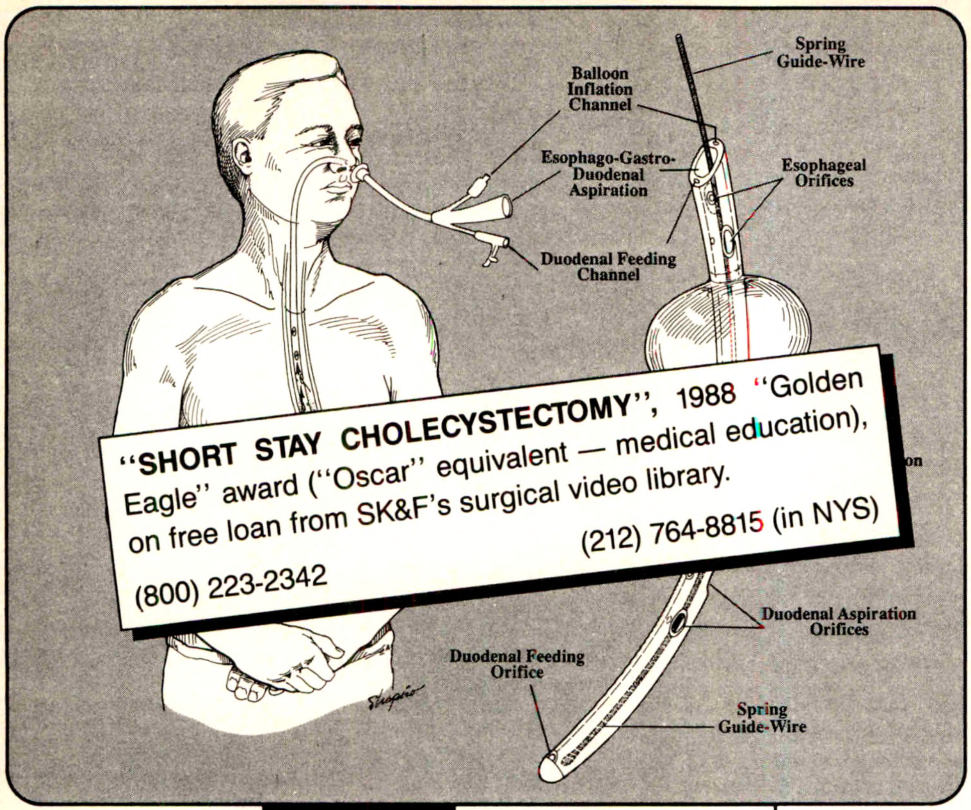

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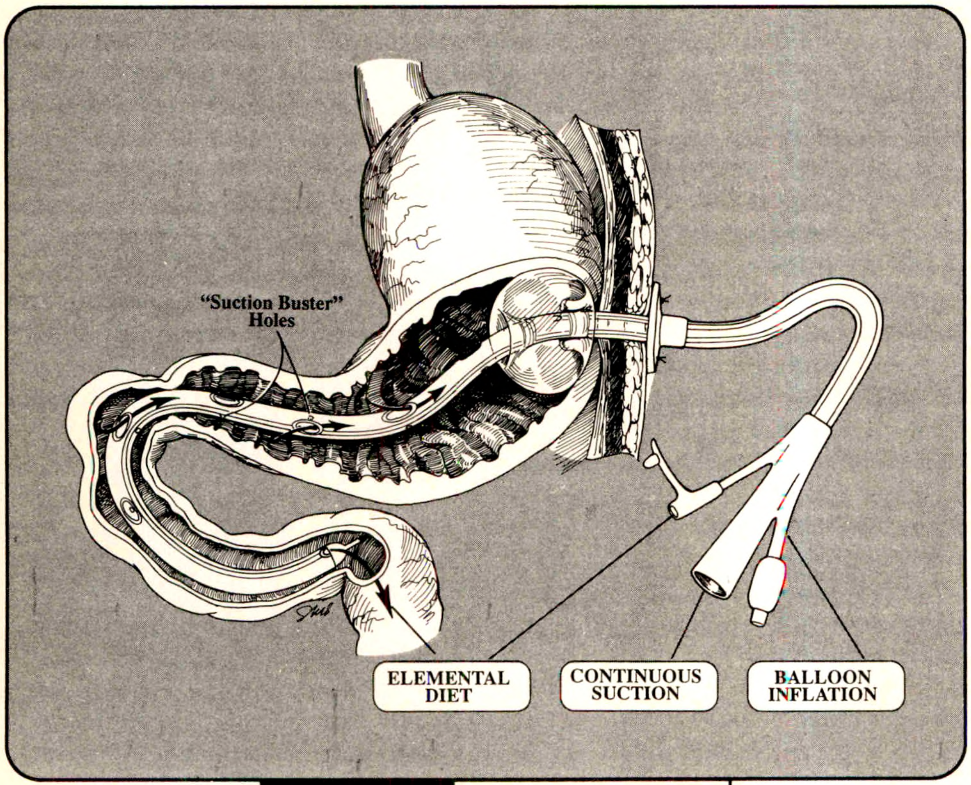

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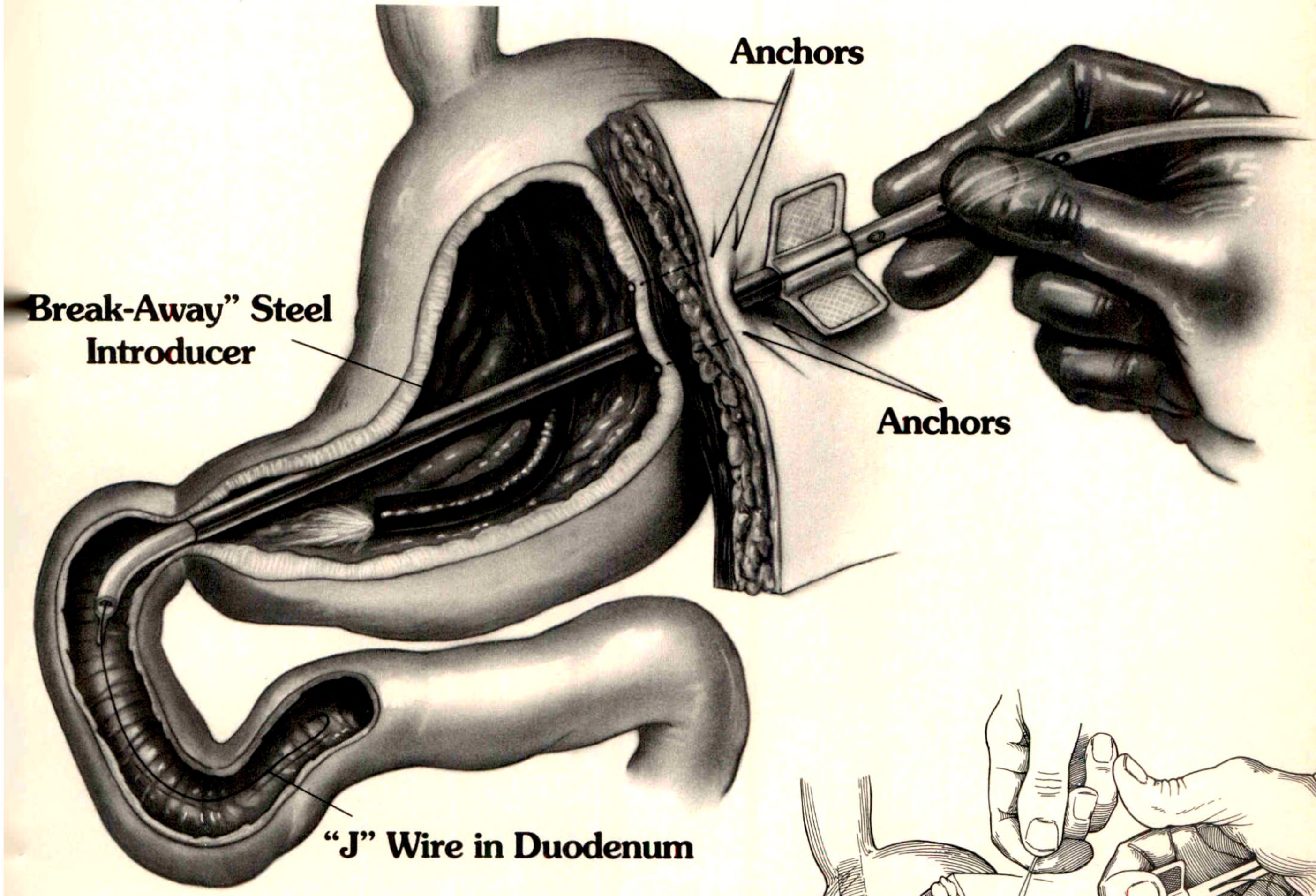

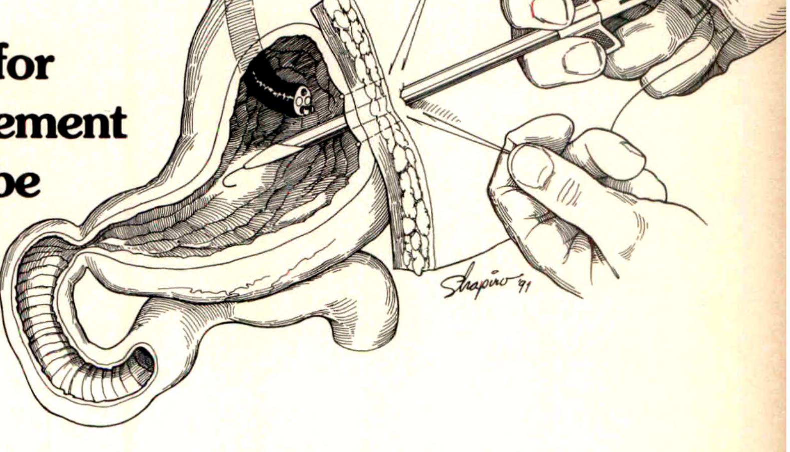

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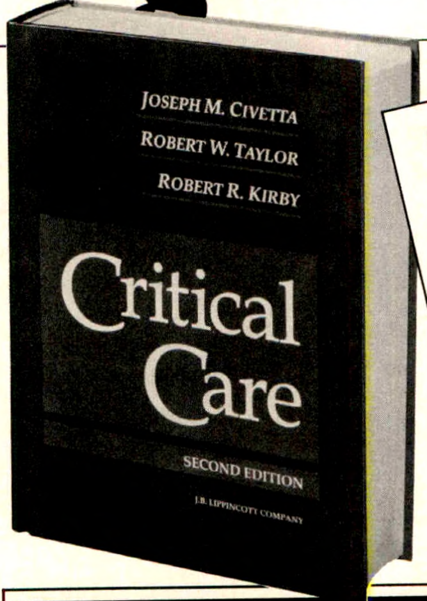

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Control of the Hypermetabolic Response to Burn Injury Using Environmental Factors

FRED T. CALDWELL, JR., M.D., BONNY H. WALLACE, M.H.S.A., JOHN B. CONE, M.D., and LINDA MANUEL

This study was performed to establish the relative efficiency of occlusive dressings and variable ambient temperature (group I) *versus* no dressings and variable ambient temperature (group II) *versus* no dressings and electromagnetic heaters (group III) for controlling the postburn hypermetabolic response. Fifteen burn patients and five normal controls (group IV) were studied when subjectively comfortable using partitional calorimetry, after which each patient was cold stressed by sequentially decreasing external energy support, and repeating calorimetry studies and serial plasma catecholamine assays. The percentage increase in heat production above predicted normal values was significantly increased for all groups when cold (C) *versus* neutral (N) (group I: [N] 24 ± 24 *versus* [C] 49 ± 25%; group II: [N] 46 ± 35 *versus* [C] 74 ± 47%; group III: [N] 21 ± 20 *versus* [C] 78 ± 25%; group IV: [N] −9 ± 12 *versus* [C] 16 ± 10%, $p < 0.05$ all comparisons). Plasma catecholamine values did not increase significantly when patients were subjectively cold. These studies do not support the role of catecholamines as the primary mediator in the cause of the postburn hypermetabolic response. Using the patients' subjective comfort status as a guide for external energy support, it is possible to greatly reduce but not to eliminate the hypermetabolic response to burn injury.

From the Department of Surgery, University of Arkansas Medical Sciences Campus, and Arkansas Children's Hospital, Burn Center, Little Rock, Arkansas

THE CLINICAL HYPERMETABOLIC response (HMR) to burn injury, first described by Cope et al.[1] in 1953, remains a critical management problem for patients with major burn injury. Early aggressive burn wound management, whether total excision within 72 hours postburn, or sequential excision and grafting does not eliminate the HMR, and may increase the importance of any measure that can control or minimize the HMR. Our current position is that the major portion of the HMR is secondary to increased heat loss, mainly evaporative, but also by radiation when such patients are cared for without dressings.

The work of Arturson[2] and our own earlier work[3] indicate that the major portion of this response can be eliminated by external heat support from electromagnetic heaters or occlusive dressings with insulative value.

This prospective study was performed to determine heat balance for patients with burn injury to more than 30% of the body surface area. Patients were managed with three currently used forms of wound care: (1) occlusive dressings with the ambient temperature (T_A) selected by the patient for subjective comfort; (2) no dressings and a comfortable ambient temperature selected by the patient; (3) no dressings and electromagnetic (EM) heaters set for patient comfort. The goals were to: (1) establish the zone of thermal neutrality for each patient; (2) examine their responses to sequentially applied cold stress, compared with each other and the five controls; (3) determine the effect of the three treatments on plasma catecholamines (epinephrine [E], norepinephrine [NE]), with the patients at a neutral environment, and sequentially during cold stress.

Materials and Methods

The study population consisted of five normal controls and 15 children and adults (without inhalation injury), 12 of whom had burn injury to 30% or more of their body surface area, admitted to the Arkansas Childrens Hospital Burn Center. Patient demographics are summarized in Table 1. Inhalation injury was defined as deficit pulmonary function severe enough to require continual endotracheal intubation and ventilatory support after the fifth postburn day. Patients were entered into the study on a

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Address reprint requests to Fred T. Caldwell, Jr., M.D., University of Arkansas Medical Sciences Campus, 4301 West Markham Street, Department of Surgery, Mail Slot 520, Little Rock, AK 72205.

Accepted for publication December 24, 1991.

TABLE 1. *Patient Characteristics*

Characteristic	Group I	Group II	Group III	Group IV
No. of patients	(n = 6)	(n = 5)	(n = 4)	(n = 5)
Age	22 ± 13	36 ± 13	32 ± 12	28 ± 17
% Full-thickness burn	11 ± 16	5 ± 6	22 ± 29	
% Total burn	36 ± 13	44 ± 18	54 ± 19	

Values are expressed as means ± SD. Burn groups are not significantly different by % full thickness or % body surface area burn.

random basis, using a table of preassignment. Patients who defaulted were entered into the occlusive dressing group. This produced four experimental groups:

Group I, Dressings with variable ambient temperature: These patients had their burn wounds treated with Silvadene (silver sulfadiazine; Marion Laboratories, Kansas City, MO) and occlusive dressings with insulative value estimated to be equivalent to 0.75 clo.[4] Dressings were changed daily and fresh Silvadene applied after removal of any residue. Quantitative surface cultures from multiple sites were performed twice weekly and more often when indicated by the patients' clinical course. Pain control was achieved using small intravenous doses of morphine as needed. As soon as the initial debridement and dressing was completed, the patient was moved to a room with temperature and humidity control beginning at ambient conditions of 28 C temperature and 40% relative humidity (thermal neutrality for nude man). The ambient temperature then was adjusted up or down to obtain a subjective feeling of comfort by the patient, neither warm nor cold but subjectively "comfortable."

Group II, No dressings with variable ambient temperature: These patients were managed as group I except for wound management. Wounds were cleansed with normal saline and fresh Silvadene reapplied daily. Additional Silvadene was applied to the wounds as required, 24 hours a day. Starting ambient conditions were the same as for group I. Ambient temperature was then adjusted up or down to achieve patient subjective comfort.

Group III, No dressings, with electromagnetic heater: This group had their burn wounds managed as group II. However, the ambient conditions were fixed at 25 C and 40% relative humidity, and the patients were allowed to adjust the variable output from an overhead 500-W electromagnetic heater (Aragona Medical, Inc., River Vale, NJ) until they were subjectively comfortable.

Group IV, Controls: Controls were managed as burn groups I and II.

All patients were managed by staged excision and grafting of full-thickness burn wounds as soon as the patients were hemodynamically stable, with the first operative procedure usually performed within the first 10 days. Ungraftable excised burn wounds were covered with either fine mesh gauze, allograft, or Biobrane (Winthrop Pharmaceuticals, New York, NY). Split-thickness donor sites were dressed with Biobrane. Patient treatment, in other words, operative procedures, took precedence over clinical studies. The baseline metabolic tests reported in this study were all performed before the first operative procedure. Patients were not studied during periods of acute illness or sepsis. Individual burn patients had thermoregulatory heat balance studies performed weekly whenever possible, until wound healing was obtained.

Study Sequence for Group I With Dressings

Dressing changes were performed in the evening, and at 5:00 A.M. the following morning, the patient was moved to the environmentally controlled metabolic chamber (Hotpack Corp., Philadelphia, PA), which was regulated at the patients' selected ambient conditions. A heparin lock was placed the prior evening to obtain repetitive blood samples without serial venopuncture. On the morning of the metabolic study, blood was drawn for E and NE determination, after which baseline partitional calorimetry was performed. Patients then were fed breakfast, and the T_A was lowered. After a steady state was obtained at the new temperature (as determined by the oxygen consumption rate and core [T_R] and surface temperatures [T_S]), the patient was asked whether they were warm, comfortable, or cold. At this point, a 20-minute calorimetry run was performed, after which blood was drawn for E and NE assay. This sequence was repeated until the T_A at which the patient was first subjectively cold. Depending on the patient's cooperation and discomfort, sequential lowering of the T_A was continued until the patient was no longer cooperative. The study was then terminated and the patients returned to their room. The study sequence of group II without dressings was identical to that just described for group I. The study sequence for group III without dressings, T_A of 25 C, and EM heaters controlled by the patient differed in that the metabolic chamber and the patient's room were maintained at 25 C and 40% relative humidity and the EM heaters adjusted to the setting required to obtain a comfort state for the patient. The study sequence differed in that the T_A was held constant and the EM heater output lowered in 50- to 150-W decrements. The patients' first sensation of coolness was again noted and calorimetry performed at successive decrements in EM heater output, each time after a new steady state was reached. As before, blood was drawn at the end of each calorimetry period for E and

NE assay. The study sequence for group IV controls was identical to that for groups I and II.

The methodology for the partitional calorimetry studies has been previously described in detail.[3] Catecholamine assays were performed using a radio-enzymatic assay kit (Amersham Cat-A-Kit, Arlington Heights, IL).

Differences between mean values for parameters measured or calculated for the four groups were examined for significant differences using analysis of variance. Where the value of F was significant, Duncan's multiple range test was used to detect significant differences between the individual group means. Intragroup changes in critical parameters were tested for significant differences between mean values using the paired t test. Examination was made for possible correlation between critical variables by linear regression analysis. Where positive or negative correlation was present, regressions were compared one with another using the small sample t tests for parallelism and common intercepts.[5,6] In all comparisons, the null hypothesis was rejected at the 0.05 level of probability.

These experimental protocols were approved by the Human Research Advisory Committee for the University of Arkansas for Medical Sciences, and informed consent was obtained from each patient or a guardian or spouse where appropriate.

TABLE 2. *Calorimetry When Patients Were Subjectively Neutral*

	Group			
Measurement	I (n = 6)	II (n = 5)	III (n = 4)	IV (n = 5)
H_P	58 ± 9	63 ± 15	61 ± 11	41 ± 5
% ΔH_P	24 ± 24	46 ± 35	41 ± 19	−9 ± 12
H_P-fever	52 ± 9	55 ± 12	53 ± 9	43 ± 5
E_V	32 ± 15	37 ± 11	38 ± 13	15 ± 3
Q_R	33 ± 8	36 ± 5	52 ± 5*	32 ± 2
H_O	4.0 ± 1.7	4.4 ± 0.7	2.3 ± 1.6	4.1 ± 1.0
T_B	37.4 ± 0.5	38.0 ± 0.6	37.8 ± 1.2	36.1 ± 0.2
T_S	32.9 ± 0.8	35.9 ± 1.2	35.8 ± 1.3*	33.6 ± 0.3
T_A	26.0 ± 1.6	28.6 ± 1.9	(25)	26.9 ± 0.8
T_R	38.1 ± 0.5	38.5 ± 0.5	38.3 ± 1.1	36.7 ± 0.3
ΔS	−0.2 ± 0.4	0.3 ± 3.5	−0.4 ± 0.5	0.6 ± 2.0
EMH	NA	NA	4.3 ± 4.4	NA

All heat production and heat loss measurements are expressed as W/m², and all temperatures as degrees Centigrade. Values are expressed as the mean ± SD.

H_P: heat production; % ΔH_P, % change in heat production when compared with predicted normal values for age and sex where the predicted normal value for group I = 48 ± 6, group II = 43 ± 3, group III = 43 ± 2, group IV = 45 ± 5[7]; H_P-fever, heat production corrected for elevation in body temperature; E_V, evaporative heat loss; Q_R, radiation heat loss; H_O, skin-to-air heat transfer coefficient; T_B, 80/20 weighted body temperature; T_S, average surface temperature; T_A, ambient temperature; T_R, rectal temperture; ΔS, stored body heat; EMH, electromagnetic heater setting, where a setting of 9 = 500 watts. (% Equation balance where heat production = heat loss: group I = 12%↑; group II = 16%↑; group IV = 15%↑.)

* Estimation of Q_R and T_S for group III is distorted by the effect of electromagnetic heaters on skin temperature.

TABLE 3. *Calorimetry When Patients Were Subjectively Cold*

	Group			
Measurement	I (n = 6)	II (n = 5)	III (n = 4)	IV (n = 5)
H_P	70 ± 7*	75 ± 19*	77 ± 12*	51 ± 6*
% ΔH_P	49 ± 26*	74 ± 47*	78 ± 25*	16 ± 10*
H_P-fever	63 ± 4*	67 ± 16	70 ± 12	53 ± 7*
E_V	35 ± 17	39 ± 18	36 ± 15	13 ± 5
Q_R	47 ± 6	50 ± 3	56 ± 9†	52 ± 1
H_O	3.5 ± 1.2	3.8 ± 1.0	3.6 ± 1.5	4.1 ± 0.5
T_B	37.3 ± 0.7	37.7 ± 1.1	37.4 ± 1.1	35.9 ± 0.5
T_S	31.8 ± 1.5	34.1 ± 2.8	33.3 ± 2.2†	31.3 ± 1.3
T_A	21.1 ± 0.8	23.9 ± 3.3	21.8 ± 3.8	21.5 ± 2.6
T_R	38.1 ± 0.8	38.6 ± 0.9	38.3 ± 0.9	36.8 ± 0.3
ΔS	−0.3 ± 2.8	0.2 ± 1.1	−1.1 ± 1.7	−2.4 ± 3.2
EMH	NA	NA	2.8 ± 3.2	NA

All heat production and heat loss measurements are expressed as W/m², and all temperatures as degrees Centigrade. Values are expressed as the mean ± SD

H_P, heat production; % ΔH_P, % change in heat production when compared with predicted normal values for age and sex where the predicted normal value for group I = 48 ± 6, group II = 43 ± 3, group III = 43 ± 2, group IV = 45 ± 5[7]; H_P-fever, heat production corrected for elevation in body temperature; E_V, evaporative heat loss; Q_R, radiation heat loss; H_O, skin-to-air heat transfer coefficient; T_B, 80/20 weighted body temperature; T_S, average surface temperature; T_A, ambient temperature; T_R, rectal temperature; ΔS, stored body heat, EMH, electromagnetic heater setting, where a setting of 9 = 500 watts. (% Equation balance where heat production = heat loss: group I = 17%↑; group II = 17%↑; group IV = 27%↑.)

* Values are significantly greater for these patients when cold as compared with neutral (See Table 2), by paired t test.

† Estimation of Q_R and T_S for group III is distorted by the effect of electromagnetic heaters on skin temperature.

Results

Calorimetry and Heat Balance

The data for neutral studies for all groups are summarized in Table 2, and for cold studies in Table 3. Estimated heat loss exceeded heat production (Hp) for groups I, II, and IV under both neutral and cold conditions by an average of 16%. This probably reflects the inability to accurately measure average surface (T_S) and body temperature (T_B) with these experimental circumstances. The use of EM heaters for group III precludes estimation of radiational heat loss.

Heat production correlates with percent body surface area burn only for neutral studies for group II (no dressings and variable ambient temperatures [T_A]) alone and combined with neutral data for group III (without dressings with EM heaters) ($r = 0.71$, $p < 0.05$; Fig. 1).

Percent body surface area burn is positively correlated with rectal temperature (T_R) for group II both for neutral and cold measurements, and groups I, II, and III for pooled neutral measurements ($p < 0.05$ for all three regressions; Table 4 and Fig. 2).

All groups, including the controls, demonstrated a significant percent increase in the rate of Hp between mea-

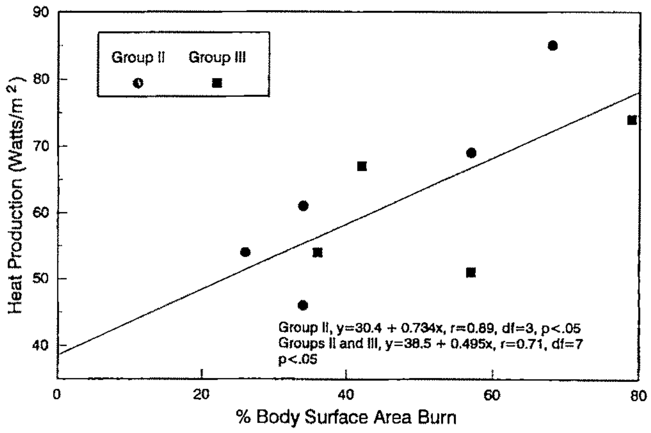

FIG. 1. Linear regression analysis of percentage of body surface area burn and heat production when the patients were subjectively neutral (groups II and III).

surements made while the subjects were subjectively comfortable as compared with when the patients were subjectively cold ($p < 0.05$ all comparisons using paired t test, see Tables 2 and 3). For burn patients with occlusive dressings (group I) while comfortable, the average increment in the rate of Hp above predicted age-matched normals from the literature[7] was 24%. When corrected for the effect of increases in T_R, the average percent increase was 10.5%. When these same patients were cold, the increments were 49% and 35%, respectively ($p < 0.002$ for values uncorrected for T_R). For patients in group II (treated without dressings and variable T_A) when comfortable, these values are 46% increase in Hp and 27% when corrected for T_R, compared with 74% and 54% when cold ($p < 0.04$). For group III (patients managed with EM heaters), when comfortable these values are 41% and 21%, compared with 78% and 61% when cold ($p < 0.05$). These data show that by using external energy support or occlusive dressings, it is possible to decrease but not eliminate the HMR to burn injury. Occlusive dressings appear to be the most efficient method for controlling the HMR, with EM heaters intermediate, and variable T_A is the least effective.

Zone of Thermal Neutrality

The mean value for preferred T_A for group I was 25.6 ± 0.9; for group II, 28.8 ± 2.1; and for group IV (controls), 27.1 ± 0.7. These data suggest that the zone of thermal neutrality after major burn injury is shifted upward when the patients are treated without dressings. The only significant difference between these groups, however, was between groups I and II ($p < 0.05$).

Plasma and Urinary Catecholamines

These data are summarized in Table 5. There were no significant intragroup differences in mean plasma E and NE concentrations comparing neutral *versus* cold values. Mean plasma E values for the two exposed burn groups were significantly higher than values for the control group for both neutral and cold conditions. Plasma E values for burn group I (with dressings) were not significantly different from values for controls when neutral or cold. Plasma E concentrations demonstrate positive correlation with Hp only for burn group II when cold. There were no significant intergroup differences in the urinary excretion rate of E, calculated for 72-hour urine collections. Mean plasma NE concentrations for exposed burn group II when neutral and cold, and exposed burn group III when cold, were significantly higher than values for controls both neutral and cold. Urinary NE excretion rates for the exposed burn groups were not different from one another, but were significantly higher than rates for the burn group with dressings and the control group. The urinary NE excretion rate for the burn group I with dressings did not differ significantly from values for the control group.

Discussion

These data support the concept that the major drive for postburn hypermetabolism is a thermoregulatory response to an increased rate of heat loss, mainly evaporative, but also radiational when patients are treated without dressings.

This portion of the HMR can most easily be controlled with insulative occlusive dressings, but also with EM heaters when patients are treated without dressings.

These data do not support catecholamines as the primary mediators of the HMR,[8] although some plasma level of at least E seems required for a maximal HMR. Changes in catecholamine metabolism after burn injury resemble

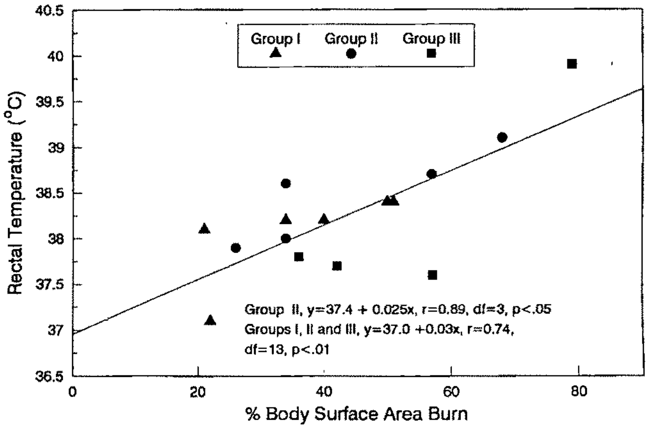

FIG. 2. Linear regression analysis of percentage of body surface area burn and rectal temperature when the patients were subjectively neutral (groups I, II, and III).

TABLE 4. *Linear Regression Analysis*

Group	Subjective Status	X Variable	Y Variable	Regression	df	r	p
I	C	T_R	H_P	Y = −195.09 + 6.96 X	4	0.82	0.04
II	N	E_VHL	H_P	Y = 17.38 + 1.22 X	3	0.92	0.02
II	N	T_S	H_P	Y = −385.43 + 12.49 X	3	0.98	0.003
II	N	T_R	H_P	Y = −1004.91 + 27.77 X	3	0.93	0.02
II	C	E_VHL	H_P	Y = 36.89 + 0.98 X	3	0.89	0.04
II	C	PE	H_P	Y = 49.88 + 0.23 X	3	0.92	0.03
II	C	%BSA	E_VHL	Y = −1.85 + 0.94 X	3	0.95	0.01
II	C	%BSA	PE	Y = −55.24 + 3.74 X	3	0.88	0.05
II	C	%BSA	T_R	Y = 36.6 + 0.05 X	3	0.94	0.02
II	N	%BSA	H_P	Y = 29.93 + 0.76 X	3	0.90	0.04
II	N	%BSA	E_VHL	Y = 11.25 + 0.60 X	3	0.94	0.02
II	N	%BSA	T_B	Y = 36.58 + 0.03 X	3	0.93	0.02
II	N	%BSA	T_S	Y = 33.19 + 0.06 X	3	0.94	0.02
II	N	%BSA	T_R	Y = 37.4 + 0.025X	3	0.89	0.05
III	C	%BSA	T_B	Y = 35.29 + 0.06 X	3	0.90	0.04

N, neutral; C, cold; %BSA, % body surface area burned; H_P, heat production; E_VHL, evaporative heat loss; Q_R, radiation heat loss; T_R, rectal temperature; T_S, average surface temperature; T_B, average body temperature (80%/20%); PE, plasma epinephrine.

a secondary general response to stress. The HMR is present in rats with burn injury after adrenal medullectomy.[9,10] Plasma values for E, the calorigenic amine, do not correlate consistently with any element of the heat balance equation. In two clinical studies, beta-adrenergic blockade produced an average reduction in the rate of Hp of 20% in one study and none in the second study.[11,12] In a third clinical study employing alpha and beta block, 64% of the original increase in Hp was still present.[8]

Elevation in T_R after burn injury is a very consistent finding, and in the current studies is directly proportional to percent body surface area burn in nonseptic burn patients (group II) both when subjectively neutral and when cold (See Fig. 2 for the neutral regression. The neutral and cold slopes of these regressions are not significantly different for patients in group II.).

Clinical studies have demonstrated increased plasma concentrations of endotoxin in burn patients for at least 1 week after burn, and during episodes of sepsis.[13,14] Interleukin-6 may remain elevated for as long as 6 weeks after burn injury and correlates well with increased T_R.[15–17]

A major portion of the increase in T_R after burn injury may represent expression of an exaggerated, prolonged acute phase response.[18,19] The role of the cytokines interleukin-1 and interleukin-6 and tumor necrosis factor in the pathogenesis of increased T_R after burn injury is only now beginning to be investigated. The frequency and importance of endotoxin, originating in the gut or burn wound, in activating fixed and circulating macrophages as well as in other cell lines to produce these cytokines, which act as internal pyrogens, continues to be studied.[20]

Thus far there is little or no evidence that these cytokines are the primary mediators of the HMR, but they may produce an additive effect to the thermoregulatory increment in Hp driven by increased heat loss, to the extent that they shift the hypothalamic thermoregulatory set point temperature upward, inducing increased T_B. By the Q_{10} effect, these cytokines further increase the rate of

TABLE 5. *Plasma and Urinary Catecholamines*

Group	Subjective Status	n	Plasma E (pg/mL)	Plasma NE (pg/mL)	Urine E (μg/m$^2\cdot$hr)	Urine NE (μg/m$^2\cdot$hr)
I, Bandaged, variable T_A	N	6	96 ± 62	663 ± 514	1.5 ± 0.7	2.3 ± 1.9
	C	6	76 ± 56	622 ± 595		
II, Exposed, variable T_A	N	5	87 ± 62	1000 ± 528	2.1 ± 1.4	5.2 ± 0.6
	C	5	108 ± 75	1274 ± 502		
III, Exposed, EMH	N	4	74 ± 25	829 ± 438	2.6 ± 1.8	7.1 ± 3.2
	C	4	130 ± 72	1135 ± 242		
IV, Controls	N	5	19 ± 11	314 ± 174	1.5 ± 0.7	1.0 ± 0.3
	C	5	18 ± 9	342 ± 158		

Values are expressed as mean ± SD.

N, neutral; C, cold; E, epinephrine; NE, norepinephrine; T_A, ambient temperature; EMH, electromagnetic heater. Urinary catecholamines were estimated on individual 72-hr urine collections made with the patients in a neutral environment.

Hp. In support of this idea, ibuprofen, which blocks the final effector limb for internal pyrogens, lowers T_B of burn patients, with an associated decrement in Hp approximately equivalent to the Q_{10} effect of lowering T_B.[21,22]

Conclusions

(1) The major drive for the postburn HMR is increased evaporative and radiational heat loss.

(2) That portion of the HMR driven by increased heat loss can be reduced to a manageable level or eliminated by using insulative dressings and ambient temperature control or no dressings with EM heaters. In both forms of management, using the individual patient's subjective perception of comfort (warmth or cold) as a guide for external energy support, it is possible to greatly reduce but not eliminate the HMR to burn injury.

(3) Catecholamines are not the primary mediators of the HMR, although some level of these amines is required for a maximal HMR.

HYPOTHESIS

A separate portion of the postburn HMR in nonseptic patients is secondary to the Q_{10} effect of a chronic increase in body temperature directly proportional to burn wound size, in response to a shift in set point temperature in the pre-optic anterior hypothalamus. This shift is mediated by the cytokines interleukin-1 or interleukin-6 by the arachidonic acid cascade and prostaglandin E.[19] Theoretically, it should be possible to manage this component of the HMR separately from that component driven by increased heat loss.

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DISCUSSION

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): Thank you, Dr. Bland, Dr. Jones, Members and Guests. I am most pleased that Dr. Caldwell has asked me to discuss this paper, because we have differed considerably in our opinions as to what causes the hypermetabolic response after a burn injury. In previous studies, Dr. Caldwell has claimed that the heat loss is the primary driving force, and in contrast, our laboratory has shown that the hypermetabolic response can be reduced by approximately 80% by feeding immediately after burn injury, at least in burned animals, and to a lesser extent, perhaps, in humans. Early feeding is associated with a marked reduction in the translocation of bacteria and endotoxin from the gut, which activates macrophages and triggers the hypermetabolic response by the release of cytokines and eicosanoids. This suggests a primary endogenous mechanism.

In the current paper, Dr. Caldwell and his associates now provide clear evidence in the comparison of three small and not necessarily comparable but very well-studied groups of burn patients that the major drive for the postburn hypermetabolic response in patients who are not at thermal neutrality and not treated with occlusive dressings is increased evaporative loss and radiational heat loss. They also suggest that if you do control thermal neutrality in a closed environment with dressings, these factors are not that important. It is indeed not surprising that increased heat production occurs in patients and even in controls who have muscle tenseness or even shivering from being cold.

They also showed that heat production correlated with the size of burn and rectal temperature. Furthermore, there was increased heat production in group 1 patients even when corrected for rectal temperature. It thus seems that the two divergent views are both correct. Increased heat production occurs in patients who are cold or have large evaporative water losses. And hypermetabolism also occurs because of increased cytokine production, in part triggered by translocation of bacteria and endotoxin from the gut.

I have two questions. From the large standard errors of and the means for heat production in all groups at thermal neutrality, there appeared to be great individual variations. Could some of this be a result of varied cytokine response? Or how else would you explain this? Was there variation in the time when your patients started full or complete enteral feedings, and did this influence the metabolic rate at thermal neutrality?

I certainly enjoyed the paper, and I congratulate the authors on an excellent study.

DR. BASIL A. PRUITT, JR. (San Antonio, Texas): I would like to compliment Dr. Caldwell and his associates on this interesting paper in which they confirm the earlier findings of several other investigators indicating that the increased metabolic rate after burn injury is temperature sensitive but not temperature dependent. Of particular interest is the demonstration that postburn hypermetabolism in all three groups, regardless of the method of wound care, is of lesser magnitude with current day techniques of burn care than it was in the late 1960s and early 1970s, when increases of two to two and a half times the predicted metabolic rate were commonly measured. These findings have direct application to the nutritional support required by burn patients.

Studies at our institute have indicated a correlation between circulating levels of catecholamines and metabolic rate after burn injury. Dr. Wilmore and others also confirmed that an additional cold stress, similar to that induced by Dr. Caldwell in these studies, was associated with further increase in circulating levels of catecholamines, except in those patients with massive burns in whom the pre–cold stress level was already at an apparent maximum. The average extent of burn in Dr. Caldwell's patients is rather small and it seems possible that, had he studied patients with more extensive burns and stratified such by burn size, he might have identified a similar relationship.

It would be helpful in interpreting these studies for Dr. Caldwell to provide us with additional information. He did not specify at what time after injury the measurements were made, and it is well known that the magnitude of postinjury hypermetabolism changes significantly across time. Dr. Caldwell states that patients were not studied during periods of acute illness or when they were septic, but he does not state how acute illness and/or sepsis were diagnosed, how many studies were delayed because of those conditions, or how many measurements were made in close juxtaposition to episodes of sepsis. If gram-negative sepsis occurred in a greater number of group 1 patients, that might account for a lower metabolic rate. Also of concern is the fact that the patients were fed breakfast between the time of the thermal neutral measurement and the cold measurements and it is unclear just how much of the increased heat production was due to the thermogenic effect of the ingested food. The magnitude of the temperature decrements is not specified and, if that differed between groups, the response of the patients might have differed. Because narcotics can decrease metabolic rate in burn patients, it will be important to know that the morphine doses cited on page 5 were comparable in all groups.

It is also troublesome that the catecholamine measurements were performed by commercial kits and one is left with the possibility that a high variability and lack of reproducibility of such kit-type measurements is responsible for the wide standard deviation of the measurements shown in Table 5. That is, the standard deviation of the plasma epinephrine levels in group 1 is approximately two thirds of the mean value, and the standard deviation of the plasma norepinephrine level is 76% of the mean. It would also be helpful if Dr. Caldwell could explain why the urinary excretion of epinephrine in group 4, the controls in whom the circulating level of epinephrine was one fourth that of group 1, was identical to the excretion in group 1. Did the patients in group 1 have some element of renal failure or hypovolemia otherwise undetected? Also of concern is the fact that the plasma epinephrine and plasma norepinphrine levels in both the thermal-neutral and cold-stressed conditions of all three groups are more than four times and two times those in the control groups, respectively. That in itself would suggest that the catechols, although perhaps not the sole mediators, are indeed mediators of postburn hypermetabolism. The lack of statistical significance of those differences may simply reflect the small number of study patients and represent a Type II error. Lastly, the attribution of hypermetabolic consequences to cytokines and arachidonic acid metabolites is puzzling because none of those substances were measured in this study.

I compliment the authors again on documenting the magnitude of postburn hypermetabolism, demonstrating how that can be modified by wound care, and redefining the principle of the overcoat.

DR. FRED T. CALDWELL, JR. (Closing discussion): One could anticipate the nature of Dr. Pruitt's remarks; however, most of his questions are answered in the manuscript, which he had for 2 weeks before the meeting. The groups are not perfectly matched but are not significantly different from one another in any critical parameter (Table 1). As in our earlier studies (Ann Surg 1981; 193:579–591), percent body surface area burn (%BSAB) did not correlate with heat production (H_P) for the burn group with dressings and variable ambient temperature (T_A), whereas the slope of the combined regression for the exposed groups for %BSAB *versus* H_P is approximately the same as in 1981. What has changed is the method of management for burn patients. Most studies demonstrating a flatter slope for the relationship between %BSAB and H_P use either occlusive dressings or external energy support (Ann Surg 1988; 208:484–492; Burns 1990; 16:259–264).

All of the calorimetry studies were performed during the first 14 days after burn, before any operative intervention, and before quantitative wound cultures exceeded 10^5 organisms/cm^2 or blood cultures were positive.

All patients and controls were fed breakfast at the same time in the study protocol. Specific dynamic action (SDA) of food may increase basal heat production by as much as 30%. It is difficult, however, to detect an SDA effect when patients with large burn wounds are studied before and after a meal. In any event, all patients and controls were treated in the same manner. We could not justify fasting these patients.

Dr. Pruitt questions the methodology for the catecholamine assay, noting great variance in the data. The radioenzymatic kit used was developed by Upjohn (Kalamazoo, MI) and sold to Amersham (Arlington Heights, IL) and has been in use for more than 15 years. All specimens were run in duplicate, against a standard curve repeated with each run. In our laboratory and in many others, this method gives results comparable to those of high-pressure liquid chromatography. Variance in this case reflects the biologic nature of catecholamines with a half-life of 20 seconds, and the true nature of human response to burn injury. In our opinion, these results reflect the relative degree of total stress experienced by the group.

Regarding norepinephrine excretion rates, there is nothing to explain. Norepinephrine urinary excretion rates for group 1 with dressings were not different from those of controls, whereas for both groups treated with wound exposure, norepinephrine excretion rates were significantly greater than for the control and bandaged groups.

We believe there are ample data to justify the hypothesis offered; it is more than speculation. Endotoxin has been demonstrated in the plasma of burn patients during the first week after burn, and during periods of sepsis (Surgery 1987; 102:808–812; J Burn Care Rehabil 1989; 10:327–330). Interleukin-6 has been demonstrated in plasma from burn patients for as long as 6 weeks after burn and positively correlates with rectal temperature. Interleukin-6 may be the most important endogenous pyrogen (Surgery 1991; 109:761–767; Lancet 1987; 2:921; Clin Immunol Immunopathol 1990; 54:361–371).

We appreciate Dr. Alexander's remarks. The role of early feeding after burn injury in preventing translocation from the gut of endotoxin and bacteria remains incompletely understood. We were unable to duplicate the results achieved by Dr. Alexander's group with early postburn feeding when we used a rat model compared with their guinea pig model (J Trauma 1990; 30[Suppl 12]S24–S30). Nonetheless, I agree that a portion of the hypermetabolic response is secondary to increased body temperature, even in nonseptic burn patients, and is driven by cytokines, most likely interleukin-6, and is mediated by the preoptic anterior hypothalamus. This is not a new idea (World J Surg 1978; 2:203–214), but new studies enhance our understanding of this complex response. Most of these patients had oral feedings begun during the first 48 hours following burn injury.

I thank the Association for the privilege of presenting these data.

Significant Trends in the Treatment of Hepatic Trauma

Experience With 411 Injuries

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Several significant advances in the treatment of hepatic injuries have evolved over the past decade. These trends have been incorporated into the overall treatment strategy of hepatic injuries and are reflected in experiences with 411 consecutive patients. Two hundred fifty-eight patients (63%) with minor injuries (grades I to II) were treated by simple suture or hemostatic agents with a mortality rate of 6%. One hundred twenty-eight patients (31%) sustained complex hepatic injuries (grades III to V). One hundred seven patients (83.5%) with grades III or IV injury underwent portal triad occlusion and finger fracture of hepatic parenchyma alone. Seventy-three surviving patients (73%) required portal triad occlusion, with ischemia times varying from 10 to 75 minutes (mean, 30 minutes). The mortality rate in this group was 6.5% (seven patients) and was accompanied by a morbidity rate of 15%. Fourteen patients (11%) with grade V injury (retrohepatic cava or hepatic veins) were managed by prolonged portal triad occlusion (mean cross-clamp time, 46 minutes) and extensive finger fracture to the site of injury. In four of these patients an atrial caval shunt was additionally used. Two of these patients survived, whereas six of the 10 patients managed without a shunt survived, for an overall mortality rate of 43%. Over the past 4 years, six patients (4.7%) with ongoing coagulopathies were managed by packing and planned re-exploration, with four patients (67%) surviving and one (25%) developing an intra-abdominal abscess. One additional patient (0.8%) was managed by resectional debridement alone and survived. During the past 5 years, 25 hemodynamically stable and alert adult patients (6%) sustaining blunt trauma were evaluated by computed tomography scan and found to have grade I to III injuries. All were managed nonoperatively with uniform success. The combination of portal triad occlusion (up to 75 minutes), finger fracture technique, and the use of a viable omental pack is a safe, reliable, and effective method of managing complex hepatic injuries (grade III to IV). Juxtahepatic venous injuries continue to carry a prohibitive mortality rate, but nonshunting approaches seem to result in the lowest cumulative mortality rate. Packing and planned reexploration has a definitive life-saving role when used adjunctively in the presence of a coagulopathy. Nonoperative management of select hemodynamically stable adult patients, identified by serial computed tomography scans after sustaining blunt trauma is highly successful (95–97%).

FOR ALMOST A quarter of a century, the overall mortality rate from civilian hepatic injuries has remained at a relatively low constant of 10%. One reason for this is that most hepatic injuries are minor (grades I to II), and require minimal or no operative intervention. Significant mortality rates, however, are associated with more complex injuries (grades III to V), often exceeding 50%.[1–6]

In 1983, the authors reported their experience with portal triad occlusion (Pringle maneuver)[7] and the finger fracture technique for achieving intrahepatic hemostasis in patients with complex injuries. We recorded a morbidity rate of 8.3% and a mortality rate of 5.3%.[4] Subsequent data accumulated over the past 8 years have corroborated this treatment modality as safe, reliable, and highly effective.

Over the past decade, however, several significant advances have evolved that radically change the way trauma surgeons approach the injured liver. These advances have been incorporated into our overall treatment plan. Foremost among them are perihepatic packing and planned re-exploration and nonoperative management of select hemodynamically stable patients identified by computed tomography (CT) scan.

The purpose of this report is (1) to present data substantiating portal triad occlusion coupled with finger fracture of hepatic parenchyma as the preferred method of managing most grade III to IV injuries; (2) to delineate

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newer trends, establish guidelines for them, and present the results of their use; and (3) to support the contention that juxtahepatic venous injuries can be managed adequately without the use of vena caval shunts.

Materials And Methods

From January 1977 to January 1991, we managed 411 consecutive adult patients with hepatic injuries at Bellevue Hospital, an Urban Level I Trauma Center. Classification of severity of injury was based on the American Association for the Surgery of Trauma hepatic injury scale[8] (Table 1).

Management of Four Hundred Eleven Hepatic Injuries

Two hundred fifty-eight patients (63%) (Fig. 1) sustained minor injuries (grades I to II), and were treated by simple suture, electrocautery, or adjunctive hemostatic agents. Fifteen of these 258 patients all died of nonrelated hepatic injuries.

One hundred twenty-eight patients (31%) sustained complex hepatic injuries (grades III to V). The specific characteristics pertaining to these patients are depicted in Table 2.

Three different treatment modalities were employed alone or in combination for the management of these 128 patients (Table 3).

Portal Triad Occlusion and Finger Fracture of Hepatic Parenchyma (121 Patients)

Group I: Grade III to IV Injuries (107 Patients). One hundred seven patients, representing 83.5% of all complex hepatic injuries, were managed by seven key maneuvers previously described[4]: (1) manual compression of the injury and intraoperative resuscitation before starting definitive operative therapy; (2) hepatocyte protection by bolus infusion of 30 to 40 mg/kg of Solu-medrol (Upjohn, Kalamazoo, MI), and the maintenance of a hepatic temperature of 30 C through topical hypothermia; (3) portal triad occlusion; (4) finger fracture of normal hepatic parenchyma in the direction of injury for ligation of lacerated blood vessels and bile ducts under direct vision; (5) resectional debridement either for severe parenchymal destruction or for removal of nonviable ischemic hepatic tissue; (6) the insertion of a viable omental pack into the liver to aid in hemostasis as well as to reduce dead space; and (7) closed suction drainage.

Eighty-six of the 107 patients (80%) were classified as grade III injuries and 21 (20%) as grade IV. In this group of 107 patients, penetrating trauma was responsible for 83% of the injuries—52 stab wounds (48.5%) and 37 gun-

TABLE 1. *Liver Injury Scale*

Grade*		Injury Description†
I	Hematoma	Subcapsular, nonexpanding, < 10% surface area
	Laceration	Capsular tear, nonbleeding with < 1-cm-deep parenchymal disruption
II	Hematoma	Subcapsular, nonexpanding, < 10–50%; intraparenchymal, nonexpanding < 2-cm-diameter
	Laceration	< 3-cm parenchymal depth, < 10-cm length
III	Hematoma	Subcapsular, > 50% of surface area or expanding; ruptured subcapsular hematoma with active bleeding; intraparenchymal hematoma > 2 cm
	Laceration	> 3-cm parenchymal depth
IV	Hematoma	Ruptured central hematoma
	Laceration	Parenchymal destruction involving 25–75% of hepatic lobe
V	Laceration	Parenchymal destruction > 75% of hepatic lobe
	Vascular	Juxtahepatic venous injuries (retrohepatic cava/major hepatic veins)
VI	Vascular	Hepatic avulsion

* Advance one grade for multiple injuries to the same organ.

† Based on most accurate assessment at autopsy, laparotomy, or radiologic study.

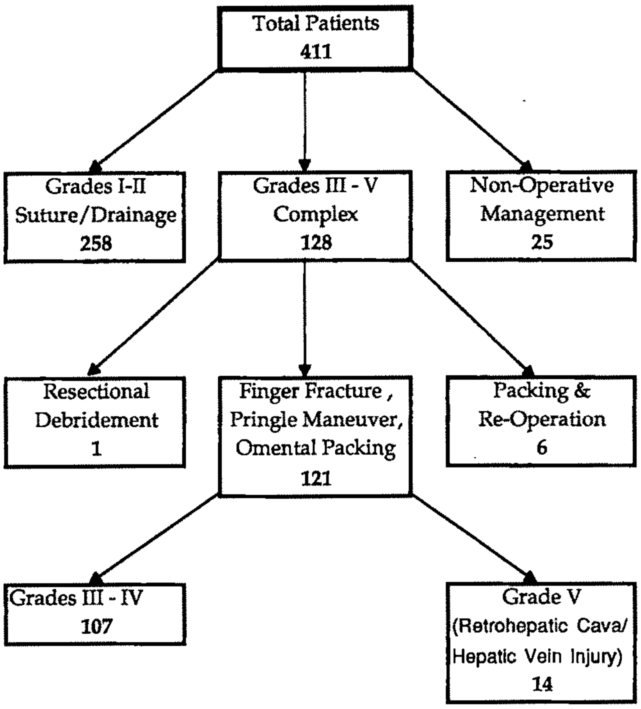

FIG. 1. Management of 411 hepatic injuries (1977–1991).

TABLE 2. *Characteristics of 128 Complex Hepatic Injuries*

75% hypotensive (systolic blood pressure <90)
60% associated injuries (25% hollow viscus)
Mean ISS score = 39 (range 16–75)
Mean transfusion = 14.5 units (range 4–60 units)
Etiology
  Penetrating 99 (77%)
    Stab wound 56
    Gunshot wound 43
  Blunt 29 (23%)

TABLE 3. *Management Techniques and Results in 128 Complex Operative Cases*

Treatment	No. of Patients	Mean ISS	Mortality	Postoperative Bleeding	Abscess	Bile Fistula
Portal triad occlusion and finger fracture						
Grade III–IV	107 (83.5%)	35	7 (6.5%)	2 (1.9%)	8 (7.5%)	6 (5.6%)
Grade V	14 (11.0%)	50	6 (43%)	—	2 (25%)	2 (25%)
Packing and reoperation	6 (4.7%)	33	2 (33%)	—	1 (25%)	1 (25%)
Resectional debridement	1 (0.8%)	16	—	—	—	—
Total	128	33.5	15 ([illegible].2%)	2 (1.6%)	11 (8.6%)	9 (7.0%)

ISS, injury severity score.

shot wounds (34%)—whereas 18 sustained blunt injuries (17%). The abbreviated injury severity score ranged from 16 to 66, with a median of 35.

Seventy-three surviving patients (73%) required portal triad occlusion to achieve intrahepatic hemostasis, with a range of ischemia time of 10 to 75 minutes and a mean cross-clamp time of 30 minutes. In 47 of these 73 (64%), the portal triad was occluded for more than 20 minutes. Moreover, occlusion time exceeded 30 minutes in 28 patients (38%) and 1 hour in 5 (7%). Liver function tests were transiently elevated in all patients during the postoperative period, but returned to normal by the time of discharge. Neither hepatic failure nor hepatic necrosis was recognized in any of these patients.

There were seven deaths, for a mortality rate of 6.5%. Two patients (1.9%), both with blunt grade IV injuries, required reoperation for bleeding in the early postoperative period. Eight (7.5%) patients went on to form perihepatic abscesses, of which two required operative drainage, and the remaining six were drained percutaneously. Six patients (5.6%) developed biliary fistulae; all, however, resolved spontaneously.

Group II: Grade V Injury (14 Patients). Fourteen patients (11%) sustained injuries to the retrohepatic cava or the hepatic veins. The abbreviated injury severity score ranged from 16 to 75, with a median of 50. Nine of these 14 (64%) resulted from penetrating trauma—five stab wounds (36%) and four gunshot wounds (28%)—and five sustained blunt injuries (36%). An atrial caval shunt was used in the initial four patients, with two surviving. One patient died before any form of operative intervention. Nine patients were managed without a vena caval shunt. Instead, prolonged portal triad occlusion (mean cross-clamp time, 46 minutes) and extensive finger fracture to the site of injury were employed. Of these nine patients, six survived. The overall mortality rate for the entire group was 43%. Of the five patients sustaining blunt injuries, however, there was only one survivor, whereas seven of the nine with penetrating injuries survived.

Two of the surviving patients went on to form postoperative subphrenic abscesses, which necessitated operative drainage in one and percutaneous drainage in the other. Two additional patients went on to form bile fistulas, both of which resolved spontaneously before discharge.

Perihepatic Packing and Re-exploration (Six Patients)

Over the past 4 years, six patients (4.7%) with complex injuries required packing and planned re-exploration to arrest hemorrhage. The abbreviated injury severity score for this group varied from 16 to 57, with a median of 35. Perihepatic packing was employed only where conventional methods failed to control bleeding, usually as a result of an ongoing coagulopathy. The method of pack insertion conformed to the technique described by Feliciano et al.[3,9] Pack removal varied from 36 hours to 4 days after operation. Four of the six patients (67%) survived, one of them going on to form an intrahepatic abscess and a biliary fistula. Both were successfully drained percutaneously.

Resectional Debridement (One Patient)

One patient (0.8%) sustaining a blunt hepatic injury was managed by resectional debridement as the primary mode of treatment.

Nonoperative Management Of Blunt Hepatic Injuries (25 Patients)

Over the past 5 years, hemodynamically stable and alert patients with blunt abdominal or lower thoracic cage injuries were evaluated by CT scanning employing a GE-9800 scanner (General Electric Medical Systems, Milwaukee, WI). All scans then were reviewed by a trauma attending physician, who made the decision for nonoperative therapy. This was based primarily on continued hemodynamic stability in an alert patient, capable of responding to serial physical examinations, coupled with the degree of injury ascertained by the CT scan.

Twenty-five patients were identified by CT scan as having either an isolated hepatic injury (23 cases), or a com-

TABLE 4. *Nonoperative Management of Blunt Hepatic Trauma in 25 Patients**

Injury Grade	No. of Patients (%)
I	7 (28%)
II	13 (52%)
III	5 (20%)

* Mean transfusion 2.2 units; mean hospitalization 14 days; success rate 100%.

bined hepatic and splenic injury (2 cases). Specific data relating to these patients are detailed in Table 4. All patients were managed initially in an intensive care unit setting. A repeat CT scan was performed at 1 week after injury. If significant resolution was achieved, patients were transferred to the ward. All patients then were rescanned before discharge and at 1-, 2-, or 3-month intervals, depending on the degree of injury resolution (Figs. 2 to 5). At the end of 3 months, virtually all lesions had resolved, and patients were then permitted to resume normal activities with the exclusion of contact sports. This mode of management was uniformly successful, and no patient required operative intervention either for failure of treatment or for the development of an abscess.

Discussion

Since 1979, the authors have advocated portal triad occlusion, the finger fracture technique, individual ligation of lacerated blood vessels and bile ducts under direct vision, coupled with extensive debridement and omental packing, for treatment of complex hepatic injuries.[10] The use of this method resulted in a mortality rate of only 5.3% in 75 patients presenting with complex hepatic injuries.[4] Of the 128 complex injuries reported in this series, 117 (91%) were managed solely by portal triad occlusion, finger fracture technique, debridement, and an omental pack. An additional 10 patients required adjunctive maneuvers (intracaval shunt in four, and packing in six) to achieve hemostasis. Thus, 127 of the 128 patients (99%) with complex hepatic injuries were managed with the techniques mentioned above. The cumulative mortality rate for these 128 patients, including those with juxtahepatic venous injuries (grade V) and those requiring packing, was 12% (15 patients). In the 107 patients with grade III to IV injuries, however, the mortality rate was only 6.5% (7 patients) with an accompanying morbidity rate of 15% (postoperative bleeding occurred twice [1.9%], eight patients [7.5%] developed perihepatic sepsis, and six [5.6%] formed biliary fistulae [Table 3]).

These successful results serve to reinforce our belief that portal triad occlusion coupled with the finger fracture

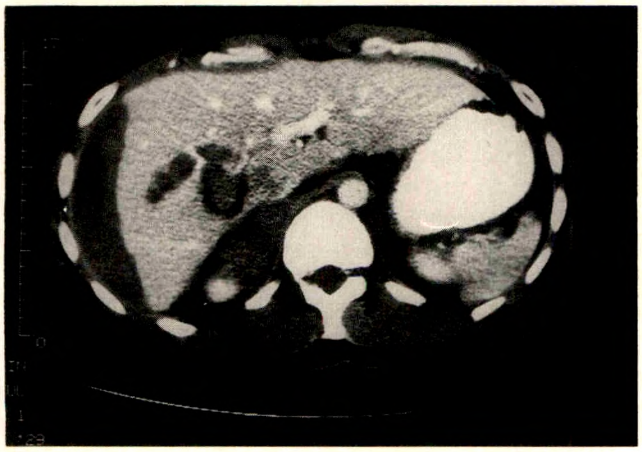

FIG. 2. A 46-year-old black man was thrown over the top of his bicycle and was brought to the emergency room. He reported right upper quadrant and right flank pain. An admitting CT scan showed a large hepatic laceration with a significant parenchymal hematoma. Because the patient was alert and hemodynamically stable, he was managed nonoperatively.

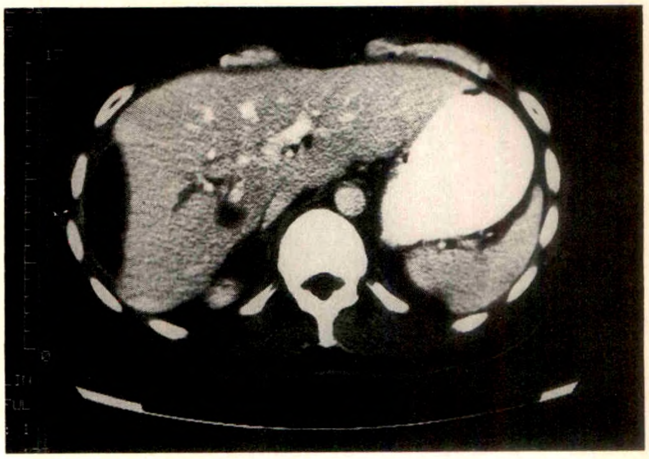

FIG. 3. CT scan 1 mo later showed significant improvement of the hepatic laceration and the parenchymal hematoma.

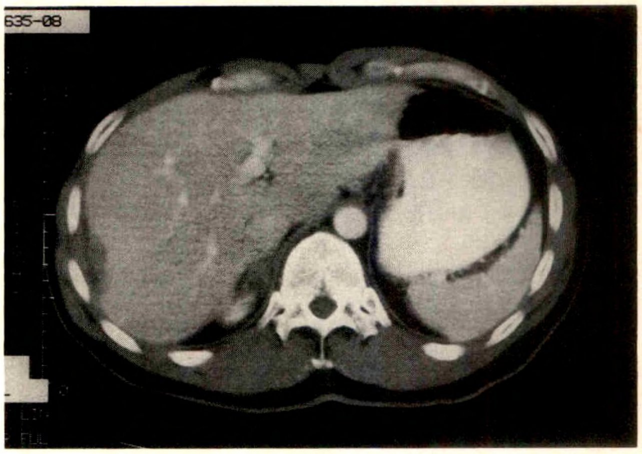

FIG. 4. Repeat CT scan 3.5 mo after injury shows complete resolution of the laceration and minimal residua of the hepatic hematoma.

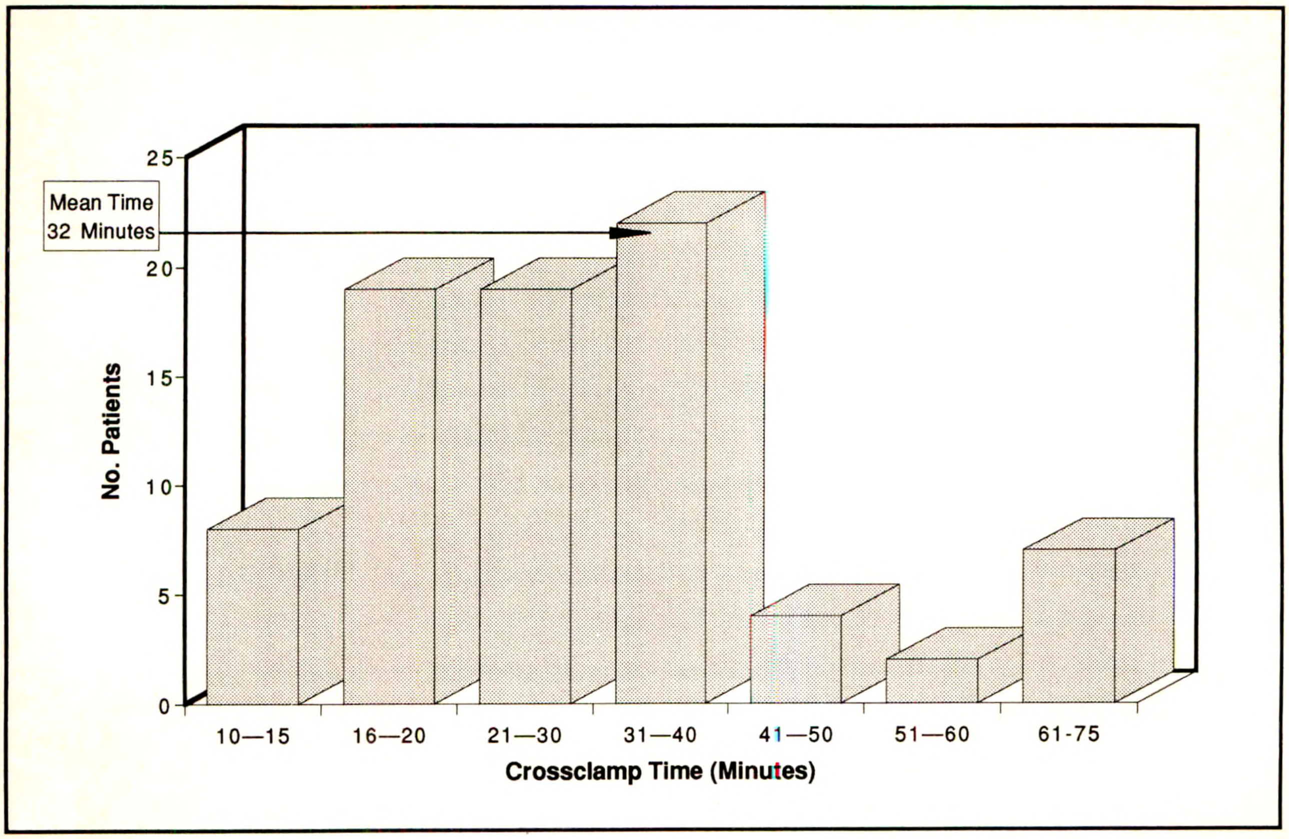

FIG. 5. Cross-clamp time: 81 patients.

technique and omental packing[6,11,12] is the optimal treatment strategy for grade III to IV hepatic injuries. Among the objections to this operative approach is the fear of excessive bleeding caused by finger fracture of normal hepatic parenchyma along nonanatomic planes[13–15] and the mistaken premise that hepatic ischemia can be safely tolerated for only 15 to 20 minutes. We have found these concerns to be entirely unwarranted. Of 128 patients in this series, 127 (99%) were managed by finger fracture of the hepatic parenchyma to the site of injury, almost always along nonanatomic planes. The fact that no major morbidity rate was incurred should dispel any fears about this approach. Acceptance of the finger fracture technique as a safe and efficient treatment modality is evidenced by its use in 45% of the complex hepatic injuries treated by Feliciano et al.,[1] and 41% of the grade III injuries reported in Cogbill's multicenter study.[2] Most recently, Beal[5] reported using this technique in 44% of 121 complex hepatic injuries, with a success rate of 87%.

As to prolonged portal triad occlusion, it would appear that despite the continued documentation of its safety during both elective and traumatic hepatic surgery,[4,10,15–19] the myth of the 15- to 20-minute time limit persists. That the human liver can safely tolerate ischemia times beyond 20 minutes is irrefutable.[4,10,15–19] The maximal limit of safe portal triad occlusion is yet to be determined. Recent data provided by Delva et al.[17] and Bismuth et al.,[18] stemming from their work with elective hepatic surgery, document warm ischemia times of up to 90 minutes, with mean cross-clamp times of 32.3 minutes and 46.5 minutes, respectively. Prolonged warm ischemia times did not adversely affect postoperative stay, incidence of hepatic failure, or mortality rate. Whether an injured liver that has sustained further damage through periods of hypotension can then undergo prolonged portal triad occlusion under normothermic conditions is unknown. For this reason we routinely use hepatocyte protection before portal triad occlusion. This concept is based on experimental and clinical data suggesting that normothermic ischemia can be extended by either regional hypothermia[20–22] or by the use of single-bolus large dose steroids (30 to 40 mg/kg Solu-Medrol).[23,24] Despite the suggestion that steroids may render patients more susceptible to postoperative sepsis,[25] this complication has failed to materialize in this series; as our abscess rate was only 8.6%.

Without randomized trials, of course, there is no hard evidence substantiating the use of either topical hypothermia or steroids as being beneficial in extending normothermic hepatic ischemia time. The authors' uniform success, however, along with the minimal complications encountered with these methods, make us decidedly reluctant to change our approach. In the current series, 81 of the 113 surviving patients (72%) with complex hepatic injuries (grades III to V) required portal triad occlusion, with a range of ischemia time varying from 10 to 75 minutes, along with the finger fracture technique to achieve intrahepatic hemostasis. The mean ischemia time for the group was 32 minutes (Fig. 5). There were no instances of hepatic necrosis or permanent hepatic dysfunction. Although the efficacy of portal triad occlusion in arresting hepatic hemorrhage has been firmly established,[4,10,19,26] there is little documentation for its use apart from the current authors. The value of this maneuver in the management of complex hepatic trauma cannot be overemphasized. Wider documentation of its use by level I trauma centers will be necessary to generate a broader database to provide the impetus necessary for acceptance of prolonged portal triad occlusion without the fear of subsequent hepatic necrosis or hepatic failure.

Retrohepatic Caval And Hepatic Venous Injuries

Injuries to the retrohepatic cava and main hepatic veins continue to result in a prohibitive mortality rate irrespective of operative management. Surviving patients have, for the most part, been salvaged by means of a vena caval shunt, usually inserted through the right atrium (atrial caval) with an ensuing mortality rate of 77%.[26] Undue delays in both prompt recognition of the injury and shunt insertion seem to predominantly be responsible for the poor results attained with atrial caval shunting.[26–28] Despite strict attention to these pitfalls, mortality rates ranging from 50% to 90% continue to be reported by major trauma centers.[14,26,31] These discouraging results with atrial caval shunts have led several investigators to attempt rapid direct exposure of the injured retrohepatic cava or hepatic veins for primary vascular repair without the concomitant use of a shunt.[26,31,32]

Among the 14 patients in this series who sustained juxtahepatic venous injuries, the initial four were managed with an atrial caval shunt, with two surviving. The next nine patients were managed without a shunt. An additional patient died before any form of therapy could be instituted. The nonshunting approach consisted of four essential features: (1) manual compression and vigorous resuscitation; (2) prolonged portal triad occlusion (mean occlusion time, 46 minutes); (3) rapid and extensive finger fracture for vascular control, almost always through normal hepatic parenchyma to the site of injury; and (4) wide mobilization of the hepatic attachments with medial rotation of the liver to provide access to both the retrohepatic cava and the hepatic vein. Six of the nine nonshunted patients (67%) survived. This experience parallels that of Buechter et al.,[31] who reported five survivors (25%) in 20 patients with juxtahepatic venous injuries. Ten of them were managed with a vena caval shunt and only one survived, whereas in the remaining 10 total hepatic vascular occlusion was employed, with four patients (40%) surviving. Similarly, Burch et al.[27] reported a 67% mortality rate in 31 patients when an atrial caval shunt was used, but only a 47% mortality rate in 15 patients (seven survivors) when the shunt was omitted. Of 142 adult patients with juxtahepatic venous injuries recorded over the past 5 years, 35 (24.6%) were managed without a shunt. The survival rate achieved in these patients was a remarkable 49%, compared with a survival rate of 19% in patients treated with shunts.[2,27,28,30,31,33]

The devastating nature of blunt juxtahepatic venous injuries is evidenced by the fact that, with rare exception, no institution can present more than one or two surviving patients.[33] Of the five blunt injuries reported in this series, only one patient survived.

Based on our own experience and that of others, several conclusions can be drawn concerning juxtahepatic venous injuries: (1) blunt injuries to these structures are almost always fatal[2,29]; (2) the cumulative mortality rate of 74% in 142 patients sustaining juxtahepatic venous injuries over the past 5 years differs little from the 77% previously reported[26]; (3) as the authors observed in 1986,[26] a direct approach to juxtahepatic venous injuries rather than using a vena caval shunt might result in better survival statistics, and this seems to be borne out in a small cadre of subsequently reported cases; and (4) advances in transplantation technology, logistical problems notwithstanding, may provide additional options in the management of these severe injuries; there has been a recent report of successful hepatectomy and second-stage transplantation.[34]

Perihepatic Packing And Planned Re-exploration

Serious complications associated with gauze packing of hepatic injuries during the early part of World War II led to the abandonment of this treatment for complex liver trauma.[35–37] When faced with threatened exsanguination from massive hemorrhage or a coagulopathy, however, packing has become an essential and lifesaving maneuver. Initial reports[19,38,39] of successful results achieved served as the basis for further investigation of this technique. Over the past decade, at least 250 documented adult patients with severe hepatic injuries were managed by packing and planned re-exploration, with 163 survivors (65%).[2,9,40–45]

In our series, six patients (4.7% of all complex injuries) were treated with perihepatic packing and planned re-exploration because of an ongoing coagulopathy. The decision for packing was made after a mean of 15 units of blood had been given and conventional attempts at repair of major lacerated blood vessels had been accomplished yet nonmechanical bleeding was evident. Four of the six patients (75%) survived who would otherwise have died. The appropriate timing for pack removal has been debated, but should logically be determined by correction of the patient's acidosis, hypothermia, and coagulopathy. For the most part these goals can be achieved within 18 to 36 hours. Packing is associated with a 20% to 30% incidence of perihepatic sepsis,[2,9,40–45] but early pack removal, along with the evacuation of intraperitoneal clots and the debridement of necrotic hepatic tissue, would appear to lessen the incidence of this problem.

Packing is most likely to be useful when a coagulopathy complicates conventional repair, or where bleeding can be specifically localized before a coagulopathy has set in.[40] When employed in this framework as an adjunctive method, a 67% survival rate has been reported in 106 patients. When it was used as a last desperate maneuver, however, only one of 47 patients (2%) survived.[2,9,45]

It should be emphasized, however, that perihepatic packing and planned re-exploration is applicable to only 3% to 5% of all hepatic injuries, because conventional techniques for controlling hemorrhage will usually suffice.

Nonoperative Management of Blunt Adult Hepatic Injuries

Nonoperative management of blunt hepatic injuries in children has been extensively documented.[46,47] The extrapolation of this approach to the adult patient, however, was initially met with scant enthusiasm, predominantly because concomitant intra-abdominal injuries could not be detected with sufficient certainty.[48,49]

Recent technological advances in the field of computerized scanning[50–53] have to some degree negated this concern. The initial success achieved by both Meyer[52] and Andersson and Bengmark[54] has subsequently been corroborated by others. At institutions nonoperatively managing 16 or more blunt hepatic injuries, at least 160 patients have been treated since 1988, with a success rate of 97%.[53,55–58]

For nonoperative management of blunt hepatic injuries to be successful, strict criteria for patient selection should be established. Patients must demonstrate (1) hemodynamic stability, either initially or through modest fluid infusions; (2) absence of peritoneal signs; (3) neurologic integrity so that frequent serial examinations by the same surgical team are possible; (4) CT scan findings consistent with a grade I to III injury; (5) absence of an associated intra-abdominal injury; (6) need for no more than two hepatic-related transfusions; and (7) CT-scan–documented stabilization or improvement of the injury.[56–58] The number of patients with blunt hepatic injuries who can be treated nonoperatively is unknown. It would seem, however, based on available published data, that at least 20% to 45% can be.[53,55–58]

Our own experience with 25 consecutive adult blunt hepatic injuries (grades I to III) managed nonoperatively (Table 4) reflects the national trend toward this newer treatment modality. Patients considered for this form of treatment should be classified as having a grade I to III type of injury. Of the 52 patients managed nonoperatively by Knudson et al.,[58] 77% were classified as grade I to III injuries. Knudson and colleagues also successfully managed 12 more hemodynamically stable patients nonoperatively, seven (13%) grade IV and five (10%) grade V injuries (60). Although their success rate speaks for itself, the routine nonoperative treatment of grade IV and V injuries may be fraught with risks even in the hemodynamically stable patient. Further data will be required to ascertain if indeed nonoperative management of highly complex injuries (grades IV to V) can be safely undertaken.

The detection of intra-abdominal injuries by CT scan has been reported to be highly accurate. This assurance notwithstanding, one must take into consideration the recent disturbing study by Croce et al.,[59] which was undertaken to correlate CT scan grading of blunt hepatic injuries and operative findings. In that study, CT scan grading correlated with operative findings in only 16%. Moreover, in 15 instances (41%) there was an underestimation of the hepatic injury. These findings seem alarming, but conversely, one wonders if the clinical course of any patient would have changed if all the criteria for nonoperative management were met and the patients were not operated on. Although the CT scan grade of injury is essential in the selection of patients for nonoperative management, the ultimate decision for operative intervention must be based on the hemodynamic stability of the patient irrespective of the grade of injury.[58] Additionally, inherent basic surgical objectives must remain of primary importance. Unnecessary blood loss increases the risk of contracting hepatitis or the human immunodeficiency virus and must be avoided. Nor must associated intra-abdominal injuries be allowed to escape detection by sole reliance on CT scanning. Serial physical examinations, preferably by the same examiner, remain essential. The commitment to treat patients nonoperatively should at no time result in the slightest hesitation to choose operative intervention if valid concerns arise.

Conclusions

Several conclusions can be drawn from our study. First, the combination of prolonged portal triad occlusion (up to 75 minutes), the finger fracture technique, and the use of a viable omental pack is, in our opinion, the optimal treatment for patients with grade III to IV injuries. This is shown by a recorded mortality rate of only 6.5% in 107 treated patients. Second, juxtahepatic venous injuries continue to carry a prohibitive mortality rate. Nonshunting approaches, however, seem at present to yield the greatest success. Third, the technique of packing and planned re-exploration has a definitive and lifesaving role when a coagulopathy is present. Fourth, nonoperative management of adult blunt hepatic injuries is highly successful (95% to 97%) in patients meeting strict criteria.

Adherence to these guidelines in the management of hepatic injuries should continue to keep mortality rates below 10% and morbidity rates to a minimum.

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DISCUSSION

DR. DAVID V. FELICIANO (Atlanta, Georgia): Dr. Bland, Dr. Jones, Members and Guests, I would like to congratulate Dr. Spencer on a very clear presentation, and also congratulate both him and Dr. Pachter on choosing me as their discussant rather than Basil Pruitt. Since his landmark presentation before this Association in 1982, Dr. Pachter has continued to educate all of us in the fine points of management of grade III, IV, and V hepatic injuries. These fine points include prolonged periods of clamping of the porta, vigorous mobilization of the injured lobe, and aggressive approach to finger fracture, which most of us now call hepatotomy, insertion of omental packing into hepatotomy sites, and a selective approach to perihepatic packing. Using this approach he has obtained enviable results, including a 93.5% survival for patients with grade III and IV injuries. In my travels around the country, I find many surgeons in the community most reluctant to adopt prolonged periods of clamping of the porta and to pursue finger fracture in a patient who already has bleeding. In essence, Dr. Pachter has emphasized an aggressive technical approach, and this is the basis for the following three questions.

First, in which patients, Leon, should the finger fracture technique not be used? For example, what do you do with a grade III hepatic injury, a through-and-through bullet wound, in a hemodynamically stable patient with only 500 mL of blood in the abdomen at operation and no active bleeding from either bullet hole? Frankly, I would do nothing with that.

Second, how often do you use the viable omental pack to truly tamponade venous oozing rather than just use it as a space filler?

And, thirdly, what drains do you use after insertion of an omental pack in a grade IV injury? This is a most comprehensive description of the state of the art in hepatic trauma, and I recommend it to the membership. Thank you for the privilege of the floor.

DR. TIMOTHY C. FABIAN (Memphis, Tennessee): Thank you. I, too, would like to congratulate Drs. Spencer, Pachter, and colleagues for an excellent review of a very large series of liver injuries. Their results in terms of perihepatic sepsis in liver-related deaths are actually very similar to what we reported here last year, although our populations are somewhat different, with theirs being 70% penetrating *versus* ours being 49%. And I think it leads us to different approaches to some degree in the management of liver wounds, because I think the mechanism of injury is very important for consideration. Your basic methods for complex injuries as described include portal occlusion, finger fracture, and omental packing. I would like to ask you to address two questions relative to that.

One, I think it is very helpful to have the Pringle maneuver applied for penetrating wounds when you have hepatic venous injuries, as well as artery and portal vein. Our experience has been not quite so good with blunt injuries, where primarily the oozing tends to be hepatic venous injuries. Could you address that?

Secondly, I think this is a grand opportunity to do a prospective evaluation to measure the effectiveness of your use of steroids and hypothermia. Clearly, steroids potentially could be harmful in this situation with multiple-injured patients with relative immunoincompetence, and they are an additional cost. We have heard a lot about hypothermia being bad for patients already this afternoon. How exactly do you pack the liver with ice, and do you think that contributes in any way to any hypothermia?

I would like to mention atrial-caval shunting for a second because it will come up year after year. Your recommendations certainly satisfy our bias relative to this. In fact, I used to believe that there were more papers on the subject than there were survivors of the procedure. But I do believe that there is, I guess, a small number of patients in whom this can be effective today. I think Jon Burch demonstrated about a 50% survival rate earlier in his paper, and other people have. Also, we have not been too anxious to use it, but I would like to hear what your current recommendations are. Should it ever be used?

And I would like to conclude the comments with addressing the nonoperative management issue. I think you should be congratulated for excellent results in 25 patients. You had no failures. I would, first of all, like to know, is that the true denominator? Is there a potential in series like this that are retrospective to a degree that some patients actually failed but went over into the operative group of management? We have had a couple of failures in our nonoperative management group that had to go to the operating room. I think that, looking at what is in the literature today, we can deceive ourselves because these are all retrospective studies. For one thing, in smaller experiences, people tend not to report bad results. I am not saying that results are other than what has been reported, but there are other people who may not have as good results and are not reporting them. And, two, they may not be recognizing that some of their surgically managed patients were indeed observed at first. I think that clearly this could only be addressed by a prospective study looking at nonoperative management very specifically and controlling your data very closely. Dr. Croce from our institution found in a report a year ago that, looking at computed-tomography (CT)-described anatomy with liver injuries, 40% of those underestimated the degree of injury, and there were some that were overestimated. It did not correlate very well at all. Consequently, what we have found now is that the volume of blood in the perihepatic tissues, gutters, and pelvis are at least as important, or maybe more important, than the anatomic description by CT scanning. If you have a grade IV injury on CT scan but no perihepatic blood, those patients generally do well. If you have some blood in the gutter, it's not quite as good. And then if you have blood in the gutter, pelvis, and perihepatic area, then there is probably a clear indication for operation regardless of grade of injury. Clearly, again, this does need more prospective evaluation. I think we'd better be a little reserved before we recommend it widely based on hepatic injury grading scale. Thank you very much.

DR. J. DAVID RICHARDSON (Louisville, Kentucky): It certainly is a pleasure to discuss this paper by Drs. Pachter, Spencer, and their colleagues. I have read the manuscript, and like the other discussants, certainly want to recommend it to anyone with a serious interest in liver trauma.

We certainly agree conceptually with virtually all of the precepts that Dr. Spencer outlined. Our experience has been remarkably similar to that which they reported, although I would like to stress that we do not use hypothermia or steroids and would again echo Dr. Fabian's call for some perhaps more scientific study of that particular treatment modality. It seems to me that most major trauma centers are now at the place where even with the difficult injuries they are hitting a mortality rate from hepatic trauma that is about in the 5% to 8% range. It may be a little higher if they are having a lot more blunt head injuries that are accounting for some of the deaths. When we reviewed our own experience, there seemed to be three things that now are limiting further progress in terms of lessening that mortality rate. We still find an occasional patient in whom the liver is pulped. That is usually either from a high-velocity gunshot wound or from blunt trauma in which literally the entire liver is in pieces, and the patient from any kind of a technical standpoint as near as we can tell is nonsalvageable. Secondly, coagulopathy has been mentioned. And I think certainly in the patient who has multiple vascular injuries in association with hepatic injury, that is a real problem and one that needs to be considered, as several papers have indicated today. And, thirdly, there is the grade V injury, which certainly limits progress in reducing mortality rate further.

Now the use of the atrial-caval shunt has been mentioned a lot in the literature, and I am convinced that Dr. Fabian is right, that there literally have been more references to it than there are survivors. There were about 44 survivors reported in a collected series a couple of years ago, if my memory serves me correctly, and I found about 300 references to the technique in various writings. I really think that the use of the atrial-caval shunt in many patients creates a disease in itself. It opens up a cavity that may not need to be opened, and even if one is applying this technique very rapidly and is familiar with it, I am not really sure that it is going to lead to improved survival. We have a couple of survivors, but generally most of the patients in whom we have used it do not survive.

I am reluctant to mention packing again because we have talked about it a couple of times, and I came in from the bathroom and the cardiac surgeons were out in the back saying, "Well, if those general surgeons would just learn how to cut and tie and sew well, they wouldn't have to pack everything." But, I will say it anyway, I do think that even in those grade V injuries there is a role for packing. We have had four survivors that I really do not believe would have survived with atrial-caval shunts, who survived by the use of selected packing of suprahepatic space. Two of those patients on reoperation required venorrhaphy or cavorrhaphy, but two actually had their bleeding totally stopped so that we just judiciously slipped the packs out, had no bleeding, put a drain in, and closed the patient. We strongly advocate when we pack that in most patients we use some kind of a vent for abdominal pressure such as Marlex (Phillips Petroleum) or a silo if one wants to use that phrase.

We think that the use of suprahepatic packing, obviously, is going to apply to an extremely small number of patients. But again, when you are down to a 5% percent mortality rate, salvaging a few more of those we hope may take us down in the range of a 2% to 3% mortality rate from the hepatic trauma itself. Thank you very much.

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): I rise primarily to focus on that group of patients who were treated nonoperatively. Dr. Spencer and his group have characteristically cut to the essence of the management of these seriously injured patients. I would like them to take us one step further. Dr. Spencer has emphasized the importance of finger fracture and also the importance of clamping across the major vessels in the liver. And I think there is no question but what that has taken us an important leap forward in the management of these patients. Is it true that only 6% of this group of patients could be treated nonoperatively? More than a decade ago, we learned in our pediatric trauma centers that it was possible to treat most of those children with blunt injuries, both with liver and with spleen injuries, nonoperatively, which was both heretical at the time and took some of us quite a while to accept. But I believe that it is possible to increase the number of those nonoperatively treated patients who have nonpenetrating injuries beyond 6%.

The question I would like to ask in closing is, what are you using as your evidence of hemodynamic instability? You mentioned, 2 units of blood. There are other better parameters of hemodynamic stability. One of the criteria that we have used in children is the relative amount of volume replacement, namely, 40 mL/kg, usually of crystalloid rather than blood. By the time blood is hung, the patient is usually on the way to the operating room. Can you give us a better idea of how you are evaluating those patients? I suspect that you will agree that a number of those patients after exploration could have been treated nonoperatively. Can you take us that next step in this group of patients to decrease operative intervention in the largest group of your patients? Finally, are you using diagnostic peritoneal lavage at all? With your good computed tomography scans, you do not really care whether there are red cells in the abdomen. And yet across the country DPL is still being used as a primary indication for exploration. Should it be abandoned? Thank you very much.

DR. H. LEON PACHTER (Closing discussion): Perhaps, I should go backwards and answer Dr. Haller's questions first. The 6% you refer to represents 6% of the entire group of patients. If one examines only blunt injuries, however, then the number of patients treated nonoperatively rises to 45%. Additionally, this is a very recent treatment modality in the adult patients, and as such I agree that the number of patients treated this way in the future will rapidly increase, if data continue to confirm the safety of this approach. With regard to what constitutes hemodynamic stability, I can only state that persistent hypotension (blood pressure <90 mmHg) in the face of moderate fluid resusitation is my definition, and if that occurs, I'm on my way to the operating room. In the hemodynamically stable patient I agree with Dr. Haller that CAT scanning is preferable to DPL.

Dr. Feliciano, as to which patients should not be treated by the finger fracture technique, I would submit the following: Patients sustaining Grade I to II injuries certainly don't; patients with Grade III injuries not bleeding too rapidly might not, but most will; Grades IV to V injuries, as I treat them, will invariably require finger fracturing. As to what I would do with a through-and-through gunshot wound of the liver with 500 mL of blood in the peritoneal cavity and no active bleeding? I know what Dr. Fabian would do. He would stick a piece of omentum in it, Dr. Stain in California would put big sutures through the injury, and in Colorado some would fill the gap with either a bunch of Penrose drains or some sort of balloon tamponading device. My approach, which seems quite radical, may in fact be the simplest method of ensuring hemostasis as lacerated blood vessels are ligated under direct vision. The Pringle maneuver, however, remains the cornerstone of this approach. Unfortunately, Dr. Feliciano, you are quite right in pointing out the great reluctance for the routine use of portal triad occlusion when confronted with complex hepatic injuries. I hope that the data presented here today will dispel once and forever the myth that portal triad occlusion beyond 15 to 20 minutes is unsafe. In answer to your second question, I use the omentum 75% of the time to tamponade minor venous oozing, and I always use it in an attempt to decrease dead space. Finally, the issue of drains seems appropriate, especially in the presence of Dr. Sparkman, who is in the audience today. In 1954, Dr. Sparkman questioned whether routine drainage of hepatic injuries were necessary, based on his experience of 100 patients. A quarter of a century later, the controversy was revived, and a final concensus has not been reached as to if, when, and what kind of drains should be used. Last year at this very meeting, Dr. Fabian presented data from a randomized prospective study comparing no drains to closed suction drains, and no drains to sump drains. The results were as follows: The incidence of postoperative abscess was 3.5% in those that had closed suction drainage, 6.7% in those with no drains, and 13% in those that had sump drains. Based on my own experience and that of Dr. Cogbill's multicenter study (J Trauma 1988; 28:1433–1438) along with the above data, I believe that some form of drainage (closed suction) is necessary for some Grade III and all Grade IV to V injuries.

Dr. Fabian, you are absolutely correct in emphasizing the fact that in blunt injuries oozing tends to be hepatic venous rather than arterial. The use of the Pringle maneuver in this situation enables me to finger fracture to the site of hepatic venous oozing while cutting off arterial inflow into the liver, thus creasing the amount of hemorrhage encountered during this maneuver. I would also like to state that I would be most enthusiastic about collaborating in a multi-institutional prospective study evaluating the effects of steroids and hypothermia in prolonging ischemia time to the liver. As far as juxtahepatic venous injuries are concerned, preliminary data suggest that results without a shunt seem to be superior to shunting procedures. Personally, I have only used a shunt once in the last 7 years, and that was subsequent to the data submitted here today. I agree that caution should be exercised when treating patients nonoperatively because one cannot sit back and rely on CAT scan findings only. The hemodynamic stability of the patients and the ability of the same set of examiners to serially follow the patient is of utmost importance.

Dr. Richardson, I enjoyed your comments about packing, particularly with regard to its relevance to patients with juxtahepatic venous injuries who previously would have been treated by atrial caval shunting. Your observations are similar to those of Dr. Beal (J Trauma 1990; 30:163–169), who reported four patients with retrohepatic caval injuries who were packed and the bleeding stopped. She then went on to insert a shunt, and all four patients died. As you suggest and I concur, there is a definitive role for packing in Grade V injuries, cardiac surgery comments notwithstanding. I would like to thank the society for the privilege of the floor.

Enteral *Versus* Parenteral Feeding

Effects on Septic Morbidity After Blunt and Penetrating Abdominal Trauma

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To investigate the importance of route of nutrient administration on septic complications after blunt and penetrating trauma, 98 patients with an abdominal trauma index of at least 15 were randomized to either enteral or parenteral feeding within 24 hours of injury. Septic morbidity was defined as pneumonia, intra-abdominal abscess, empyema, line sepsis, or fasciitis with wound dehiscence. Patients were fed formulas with almost identical amounts of fat, carbohydrate, and protein. Two patients died early in the study. The enteral group sustained significantly fewer pneumonias (11.8% *versus* total parenteral nutrition 31.%, $p < 0.02$), intra-abdominal abscess (1.9% *versus* total parenteral nutrition 13.3%, $p < 0.04$), and line sepsis (1.9% *versus* total parenteral nutrition 13.3%, $p < 0.04$), and sustained significantly fewer infections per patient ($p < 0.03$), as well as significantly fewer infections per infected patient ($p < 0.05$). Although there were no differences in infection rates in patients with injury severity score < 20 or abdominal trauma index ≤ 24, there were significantly fewer infections in patients with an injury severity score > 20 ($p < 0.002$) and abdominal trauma > 24 ($p < 0.005$). Enteral feeding produced significantly fewer infections in the penetrating group ($p < 0.05$) and barely missed the statistical significance in the blunt-injured patients ($p = 0.08$). In the subpopulation of patients requiring more than 20 units of blood, sustaining an abdominal trauma index > 40 or requiring reoperation within 72 hours, there were significantly fewer infections per patient ($p = 0.03$) and significantly fewer infections per infected patient ($p < 0.01$). There is a significantly lower incidence of septic morbidity in patients fed enterally after blunt and penetrating trauma, with most of the significant changes occurring in the more severely injured patients. The authors recommend that the surgeon obtain enteral access at the time of initial celiotomy to assure an opportunity for enteral delivery of nutrients, particularly in the most severely injured patients.

DESPITE DIAGNOSTIC AND therapeutic advances available to physicians, sepsis remains the most common problem in critically ill patients. The hypermetabolic state induced by these complications gradually depletes the body of fat and protein stores. This progressive protein-calorie malnutrition increases the rate and risk of infection[1] and impairs wound healing.[2] Over the past 2 decades, significant amounts of clinical and laboratory research have focused on the role of specialized nutrition support in preserving lean tissue mass and host defenses. Although clinicians agree that the gastrointestinal (GI) tract is the preferable route for nutrient administration, patients are often provided total parenteral nutrition (TPN) because of ease and reliability of administration. Unfortunately, this "traditional" approach has been no panacea for the critically ill, and few studies demonstrate significant benefits on morbidity and mortality rates with TPN.

A substantial body of data suggests that route of nutrient administration influences the response to injury. The normal well-fed intestine absorbs nutrients while maintaining an effective barrier against intraluminal toxins and bacteria. Peristalsis, secretory immunoglobulin A, mucin, and the mucosa have protective and supportive roles in maintaining this function.[3] Proponents of enteral (ENT) feeding cite expense, preservation of gut mass,[4] and positive effects on the metabolic, hormonal,[5] immunologic,[6] and visceral protein responses to injury with feeding[7] but these arguments are countered by difficulty with delivery of adequate nutrients by nasoenteric feeding and the rare but possible risk of life-threatening complications. Direct ENT feeding by jejunostomy provides a more reliable means of ENT access and intestinal feeding that bypasses the problem of delayed gastric emptying. Although laboratory[8,9] and prospective clinical trials[10,11] confirm reduced morbidity and mortality rates after trauma when

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nutrients are provided through the GI tract rather than intravenously (I.V.), many clinicians remain skeptical of this route of administration.[12] Unfortunately, in the few randomized prospective studies to date, the most severely injured patients such as those requiring early reoperation, massive blood transfusions, or those with extensive intra-abdominal injuries with an abdominal trauma index (ATI)[13] of greater than 40 have been excluded from analysis.[10,11] If ENT feeding is truly beneficial, the most critical patients should be included in the study population.

This randomized prospective study examines the effect of early ENT *versus* early parenteral feeding on the outcome of trauma patients in the first 15 days of hospitalization. Using these two standard feeding techniques, outcome variables included the amount of nutrition delivered, septic morbidity rates, and clinical outcome in a population of consecutive trauma patients with an ATI ≥ 15 treated at an urban level I trauma center.

Materials and Methods

Study Protocol

Ninety-eight trauma patients admitted to the Presley Memorial Trauma Center at the University of Tennessee, Memphis, requiring an emergent laparotomy between December 1989 and August 1991, were enrolled in the study protocol. Patients 18 years of age or older, with an intra-abdominal injury requiring laparotomy, who sustained an ATI of at least 15, were included in the study. After the management of intra-abdominal injuries, jejunostomy tubes were inserted distal to the ligament of Treitz using either a needle catheter jejunostomy (Vivonex Kit, Norwich-Eaton Pharmaceuticals, Norwich, New York) or standard red rubber catheter chosen at the discretion of the five trauma service surgeons. Within 8 hours after operation, the Nutrition Support Service of the Regional Medical Center of Memphis was consulted and patients were assigned to either ENT or TPN feeding using a randomization table generated by computer before institution of the study. Patients were not excluded from the study because of excessive blood loss, the need for reoperation within the first 72 hours, or an ATI of 40 or greater. Patients with intestinal repairs or anastomosis were included in the study. All postoperative management was directed by three of the operating surgeons responsible for trauma intensive care unit care. The study design and consent was approved by the Institutional Review Board of the University of Tennessee, Memphis.

Non-nutritional management of patients for both intra- and extra-abdominal injuries remained standard for our institution throughout the study. Patients sustaining blunt or penetrating trauma were explored for signs of peritoneal irritation or hemodynamic instability from continued intra-abdominal bleeding. Standard diagnostic peritoneal lavage criteria were used (red blood cells ≥ 100,000/mm^3, white blood cells > 500/mm^3, presence of fiber, bacteria, or bile) to assess abdominal injury. When computed tomography scans were performed to evaluate blunt abdominal trauma, patients were explored for class III or higher liver and spleen injuries. Patients with gunshot wounds that traversed the abdominal cavity or knife stab wounds that penetrated the anterior fascia underwent celiotomy. Perioperative broad-spectrum antibiotics were administered prophylactically to all patients for no more than 5 days unless clinical evidence of infection ensued or prophylactic antibiotics were dictated by the specialty services. Skin and subcutaneous tissue were left open for delayed primary closure in the presence of fecal and significant gastric contamination.

Both ENT and parenteral nutrients available to the clinician at the Regional Medical Center at Memphis are determined biannually by a bidding process that defines the formulary for nutrient products. The ENT formula (Vital HN, Ross Laboratories, Columbus, OH) administered to patients in this randomized, prospective study was chosen because it was the low-bid ENT product at the start of this study. For pair feeding purposes, the pharmacy provided a parenteral formula with similar concentrations of protein (Travasol, Clintec Nutrition, Deerfield, IL), carbohydrate, and fat (Intralipid, Kabivitrum, Inc., Alameda, CA) (Table 1). Institution of full-strength formulas progressed toward a goal rate of 1.5 to 2.0 g/kg/day of protein/amino acids and 30 to 35 Kcal/kg/day of nonprotein calories (NPC). The time from injury to institution of feeding was noted, and the rates of ENT and TPN feeding advanced as tolerated by the clinical condition of the patient. Eight patients with coagulopathy and uncontrollable intra-abdominal bleeding had temporary packing of their intra-abdominal injury and subsequent correction of hypothermia, acidosis, and coagulopathy in the intensive care unit. These eight patients were returned to the operating suite within 24 to 48 hours for completion of their operations and placement of ENT feeding tubes and they were subsequently randomized to either ENT or TPN feeding.

Nasogastric decompression continued for at least 3 days. Nursing personnel flushed jejunostomy tubes with 10 cc of saline every 8 hours and administered no med-

TABLE 1. *Composition of Enteral and Parenteral Formulas*

	Enteral	Parenteral
Protein/amino acids	16.7%	17%
BCAA	18.2%	15.6%
CHO	73.9%	74%
Fat	9.4%	9%
Calorie/nitrogen	150/1	150/1

BCAA, branched-chain amino acids; CHO, carbohydrate.

ications other than tube feeding through the jejunostomy. The sole exception to this protocol occurred in six (four TPN/two ENT) patients with *Candida* colonization at multiple sites. In those patients, nystatin was administered through the jejunostomy catheter and immediately flushed with 10 mL saline. Central venous catheters were changed over a guidewire every 3 days, and the catheter tip and subcutaneous portions were sent for semiquantitative cultures. Twenty-four–hour urine collections were obtained on days 1, 4, 7, and 10 from the first 25 patients admitted to the trauma intensive care unit. Venous blood sampling for SMA-24 was obtained on the same days. The operating surgeon calculated the ATI at the time of the initial jejunostomy placement. Nursing personnel of the Trauma Center Registry calculated the Injury Severity Score (ISS) to provide an anatomic index of the severity of total body injury.

Septic morbidity was defined as pneumonia, intra-abdominal abscess (IAA), empyema (EMP), or line sepsis during the first 15 days. Septic morbidity was limited to 15 days for several reasons. Sixty-two (64%) patients had been discharged from the hospital by that time. Of the remaining patients, most who developed pneumonias, IAAs, or EMPs had developed this complication within the first 2 weeks. Late septic complications that might have developed were related to orthopedic complications, recurrent urinary tract infections, or recurrent pneumonia. There is no reason to expect that early ENT feeding would have any effect on these complications.

Pneumonia was defined as fever, leukocytosis, positive sputum/bronchoalveolar lavage specimens, or purulent sputum with the development of new pulmonary infiltrates. Atelectasis, pulmonary contusion, and pleural effusions were excluded as causes of the source of infiltrates. Intra-abdominal abscess or EMP was defined as the presence of a purulent collection in the abdominal or thoracic cavity after drainage by laparotomy, thoracostomy tube, or computed tomography–directed catheter placement. Line sepsis was defined as purulence at the exit site of the catheter or positive catheter tip cultures in association with positive blood cultures and no other obvious source of bacteremia. Patients were not discontinued from TPN because of line infection; however, the catheter was removed and nutrition was reinstituted within 24 hours by a catheter inserted into another site. Necrotizing fasciitis, and wound infections associated with wound dehiscence were considered septic complications; however, minor wound infections and urinary tract infections were not included. Diarrhea was defined as unformed, watery stool occurring three or more times per 24-hour period.

Enteral nutrition continued in ENT patients until they tolerated a diet, but two patients were switched to TPN because of failure to tolerate at least 50% of nutrient goal by 1 week. The complications of these patients were included in the ENT analysis. After the first 40 patients had been enrolled in the study, TPN patients developing pneumonia, EMP, or IAA were switched to ENT feeding after confirmation of infections. In this group also, outcome data and septic morbidity that occurred up to the time of the switch to ENT feeding was included in the TPN group data. No enrolled patients were dropped from study analysis except for two early deaths.

All infections were treated after diagnosis by the surgeons delivering the postoperative care. At the time of hospital discharge, all charts were reviewed by the principal author for confirmation of infection. The charts of those patients in whom the presence of infection was not clear were reviewed by a second surgeon blinded to therapy, and this determination was considered definitive for the presence or absence of infection. After discharge, charts were reviewed to determine length of hospital stay, number of ventilator days, number of days receiving tube feedings or TPN, number of antibiotics and number of days on antibiotics, failure of ENT nutrition requiring cross-over to TPN, number of units of blood administered in the first 24 hours and during total hospitalization, and the maximum bilirubin level occurring in the first 15 days. The amount of nutrition administered by the ENT and TPN routes was also obtained. Nitrogen balances were calculated on days 1, 4, 7, and 10 by subtracting nitrogen losses (total urinary nitrogen excreted over 24 hours) plus an estimated stool and obligatory nitrogen loss of 2 g from the total nitrogen administered during that 24-hour period. Total urinary nitrogen was calculated using the pyrochemiluminescence technique with the Antek Nitrogen Analyzer (Antek Inc., Houston, TX).

Statistical Analysis

Significance for discrete (categorical) variables was determined with the chi square test of homogeneity or Fisher's exact test; all continuous variables were tested with either t tests or Mann-Whitney U tests. Before making each t test, we tested the assumption of equal or unequal variances with an F test and used the appropriate t test. Two-way analysis of variance was used to assess differences for infected and noninfected patients, for rate per kilogram per day, and ISS and ATI scores. A repeated measures analysis of variance compared nitrogen balance over time. Kaplan-Meier estimates of the survival distribution were computed within strata for length of stay in the hospital and number of feeding days and tested for equality. Risk was estimated as the cumulative incidence among patients who developed infections during the first 15 days of hospitalization. The crude measure of association between a single potential risk factor and infection was expressed as the relative risk, or rate of risk. Logistic regression was used to evaluate results from univariate and multivariate analyses and approximate relative risk by odds ratios. For multivariate analyses, patients were stratified by presence (or absence) of a particular injury, mechanism of injury, or severity of injury (ISS or ATI score).

Results

Ninety-eight patients entered the study. One death occurred within 4 days in each of the groups due to hemodynamic instability and progressive multiple system organ failure. These two patients were excluded from analysis. Groups were well matched for severity of injury, age, and mechanism of injury (Table 2).

Although not statistically significant, more patients (31.4%) in the ENT group sustained blunt trauma than in the TPN group (22.2%). Only six patients suffered knife wounds, with four of these patients entered into the TPN group.

Enteral feeding began 24 ± 1.7 hours after surgery; TPN began 22.9 ± 1.6 hours after surgery. Two patients (3.9%) failed ENT feedings because of significant abdominal distention. One patient developed delirium tremors and significant abdominal distention, but no significant pathology was found at exploration. He subsequently suffered dehiscence of his wound and developed the only IAA in the ENT group. The second patient developed abdominal distention and failed to tolerate a minimum of 25 mL/hour, therefore I.V. feeding was begun 7 days after entry into the study. Seven TPN patients were switched to ENT feeding after developing significant infections after operation.

There were no significant differences in blood requirements during the first 24 hours, total blood administered during the hospitalization, days on a ventilator, number of antibiotics, or number of days on antibiotics (Table 3). Patients in the TPN group had significantly higher maximum bilirubin levels during the first 15 days (ENT: 1.6 ± 0.3 mg/dL *versus* TPN: 2.2 ± 0.04 mg/dL, $p < 0.05$), although no significant differences in maximum bilirubin serum concentrations were noted between either the infected ENT and infected TPN group (ENT: 3.2 ± 1.5 mg/dL *versus* TPN: 3.4 ± 1.0 mg/dL) nor between the uninfected ENT and TPN groups (ENT: 1.4 ± 0.3 mg/dL *versus* TPN: 1.6 ± 0.3 mg/dL).

TABLE 2. *Demographics and Mechanism of Injury*

	ENT (N = 51)	TPN (N = 45)	p
Age (yr)	30.4 ± 1.7	30.6 ± 1.4	NS
ATI	29.1 ± 1.8	29.1 ± 1.4	NS
ISS	25.1 ± 1.7	25.1 ± 1.9	NS
LOS (days)	20.5 ± 2.8	19.6 ± 2.8	NS
Mechanism of injury			
Blunt	16 (31.4%)	10 (22.2%)	NS
Penetrating	35 (68.6%)	35 (77.8%)	NS
Gunshot	30 (58.8%)	29 (64.4%)	NS
Knife	2 (3.9%)	4 (8.9%)	NS
Shotgun	3 (5.9%)	2 (4.4%)	NS

Mean ± SEM.

ENT, enteral; TPN, total parenteral nutrition; ATI, abdominal trauma index; ISS, injury severity score; LOS, length of stay.

TABLE 3. *Antibiotics, Blood Administration, Ventilator Needs, and Nutritional Administration*

	ENT	TPN	p
Blood (1st 24 hr)	6.1 ± 1.2 units	6.1 ± 1.2 units	NS
Blood (total)	8.9 ± 1.5 units	9.6 ± 2.1 units	NS
Ventilator days	2.8 ± 0.7	3.2 ± 1.0	NS
No. of antibiotics	2.6 ± 0.3	3.0 ± 0.6	NS
Days on antibiotics	10.9 ± 1.6	11.4 ± 2.3	NS
Nitrogen balance (mg/kg/day)*			
Day 1	−284 ± 25 (16)	−252 ± 24 (20)	NS
Day 4	−77 ± 28 (19)	−109 ± 29 (21)	NS
Day 7	−238 ± 51 (11)	−149 ± 37 (11)	NS
Day 10	−171 ± 34 (5)	−190 ± 66 (5)	NS
NPC/kg/day	15.7 ± 4.2	19.1 ± 3.3	<.05
NPC/kg at maximum rate	29.0 ± 1.5	31.7 ± 1.2	NS

Mean ± SEM.

* No. of patients analyzed for nitrogen balance shown in parentheses.

ENT, enteral; TPN, total parenteral nutrition; NPC, nonprotein calories.

There were no significant differences in nitrogen balances between the two groups on any day. Nitrogen balances became more negative during the later days of study as less extensively injured patients were transferred from the intensive care unit. Enteral nutrition patients received significantly less nutrition per kilogram per day than did TPN patients ($p < 0.05$), but no differences in maximal rates given were noted between the two groups or in the noninfected patients (ENT: 30.2 ± 1.2 NPC/kg/day *versus* TPN: 29.9 ± 15 NPC/kg/day). Infected ENT patients tended to get less nutrition during the study (ENT: 27.7 ± 2.8 NPC/kg/day *versus* TPN: 33.7 ± 1.9 NPC/kg/day), but this failed to reach statistical significance ($p = 0.09$).

Patients randomized to ENT experienced significantly less septic morbidity than patients receiving TPN. Enteral nutrition patients developed significantly fewer pneumonias, abscesses (defined as IAA or EMP) or line sepsis (Table 4). Only one patient with line sepsis did not have a simultaneous pneumonia, IAA, or EMP, so that the addition of line sepsis increased the number of infected ENT and TPN patients by one in each group. Enteral patients sustained significantly fewer infections per patient than the TPN group (0.25 ± 0.06 *versus* 0.71 ± 0.14, $p < 0.03$) as well as significantly fewer infections per infected patients (1.08 ± 0.08 *versus* 1.6 ± 0.8, $p = 0.04$). Only three ENT patients developed more than one infection,

TABLE 4. *Septic Morbidity*

Sepsis	ENT	TPN	p
Pneumonia	6/51 (11.8%)	14/45 (31%)	<.02
Intra-abdominal abscess	1/51 (1.9%)	6/45 (13.3%)	<.04
Empyema	1/51 (1.9%)	4/45 (9%)	NS
Line sepsis	1/51 (1.9%)	6/45 (13.3%)	<.05
Fasciitis/dehiscence	3/51 (5.9%)	4/45 (8.9%)	NS
Abscesses (intra-abdominal and/or empyema)	2/51 (3.9%)	8/45 (17.8%)	<.03
Pneumonia and/or abscesses	8/51 (13.7%)	17/45 (37.8%)	<.02
Pneumonia, abscesses, and/or line sepsis	9/51 (15.7%)	18/45 (40%)	<.02

ENT, enteral; TPN, total parenteral nutrition.

TABLE 6. *Frequency of Infections (Pneumonia, Intra-abdominal Abscess, or Empyema) After Stratification of Patients by Mechanism and Severity of Injury*

	ENT	TPN		
Variable	No. (%)	No. (%)	Odds Ratio	p
ISS ≤ 20	3/17 (17.7)	4/20 (20.0)		0.9
ISS > 20	5/34 (14.7)	13/25 (52.0)	6.3 ×	<0.002
ATI ≤ 24	5/24 (20.8)	7/24 (29.2)		0.6
ATI > 24	3/27 (11.1)	10/21 (47.6)	7.3 ×	<0.005
ATI > 24 and ISS > 20	3/20 (15.0)	8/12 (66.7)	11.3 ×	<0.003
Blunt	4/16 (25.0)	6/10 (60)	3.0 ×	0.08
Penetrating	4/35 (11.4)	11/35 (31.4)	3.6 ×	<0.05

ENT, enteral; TPN, total parenteral nutrition; ISS, index severity score; ATI, abdominal trauma index.

whereas 14 of 45 parenteral patients developed more than one infection (p = 0.02) (Table 5). All patients with fasciitis/dehiscence had a simultaneous pneumonia or abscess.

If one considers only the presence of pneumonia, IAA, or EMP as a source of infection, ENT feeding has its most beneficial effect in the most severely injured patients, but has little effect in less injured patients (Table 6). No significant differences in infection rates were noted in patients with an ISS of 20 or less. Of patients with a high ISS (>20), five of 34 (14.7%) of ENT patients developed an infection *versus* 13 of 25 (52.0%) of the TPN group (p < 0.002); failure to administer ENT feeding to this population of patients increased the risk of septic complications by a factor of 6.3. In patients with an ATI > 24, use of TPN was associated with a sevenfold increase in the risk of infection, with an incidence of 11.1% (3/27) with ENT feeding *versus* 47.6% (10/21) with TPN (p < 0.005). In the 32 patients with both high ISS (> 20) and high ATI (> 24), TPN usage was associated with an 11-fold increase in the risk of infection, with a 15% infection rate (3/20) with ENT feeding *versus* 66.7% (8/12) with TPN feeding (p < 0.003). Patients with blunt injuries had higher infection rates if fed parenterally (6/10; 60%) than if fed enterally (3/6; 18.8%), with TPN feeding associated with a threefold increased risk of infection, but this barely failed to reach statistical significance (p = 0.08). Enteral patients with penetrating wounds developed significantly fewer (p < 0.05) septic complications than did TPN patients, with the risk of infection increased 3.6 times in the TPN group. If infection is limited to pneumonia, IAA, or EMP, there was no difference between infected ENT and TPN groups in ATI (ENT: 30.6 ± 4.6 *versus* TPN: 34.4 ± 3.2) or ISS (ENT: 29.1 ± 4.1 *versus* TPN: 32.9 ± 2.9).

Evaluating outcome by organs injured, significant differences in the infection rates between ENT and TPN were found in patients with pancreas or liver injuries (Table 7). There was no significant difference in infection rate with treatment in patients when stratified by colon/rectal, kidney, stomach or duodenal, vascular, or splenic injuries, although both splenectomy and stomach injury approached statistical significance.

Similar trends were noted in the patients excluded from previous clinical trials (Table 8). Twenty patients recruited had an ATI ≥ 40 (n = 14; seven ENT, seven TPN), required more than 25 units of blood during the first 24 hours (n = 4; three ENT, one TPN), had a pelvic fracture requiring more than 6 units of blood (n = 3; two ENT,

TABLE 5. *Frequency of Infections*

	ENT	TPN
Number of Infections/Patient	No. (%)	No. (%)
0	39/51 (76.5)	25/45 (55.6)
1	9/50 (17.7)	6/45 (13.3)
2	0	6/45 (13.3)
3	0	4/45 (8.9)
4	3/51 (5.9)	3/45 (6.7)
5	0	1/45 (2.2)

ENT, enteral; TPN, total parenteral nutrition.
p = 0.02.

TABLE 7. *Frequency of Infections (Pneumonia, Intra-abdominal Abscess, or Empyema) After Stratification of Patients by Individual Injuries*

	ENT	TPN		
Injury	No. (%)	No. (%)	p	Odds Radio
Colon/rectum	3/21 (14.3)	5/17 (29.4)	NS	
Stomach	4/16 (25)	9/16 (56.3)	<0.08	4.0 ×
Duodenum	1/3 (33.3)	4/8 (50.0)	NS	
Pancreas	2/11 (18.2)	4/5 (80)	<0.02	18.0 ×
Liver	3/21 (14.3)	14/29 (48.3)	<0.02	5.6 ×
Spleen	0/5 (0)	3/6 (50)	<0.07	2.0 ×
Kidney	3/9 (33.3)	3/8 (37.5)	NS	
Vascular	2/12 (16.7)	2/8 (25.0)	NS	

ENT, enteral; TPN, total parenteral nutrition.

TABLE 8. *Demographic Characteristics and Outcome of Patients With ATI > 40, Blood Loss > 25 Units in the First 24 Hours, Pelvic Fracture With > 6 Units Blood Loss, or Reoperation Within 72 Hours*

	ENT (n = 11)	TPN (n = 9)	p
ATI	40.5 ± 5.9	42.7 ± 6.9	NS
ISS	22.9 ± 2.8	29.7 ± 3.9	NS
Blunt injuries	3/11	2/9	NS
Penetrating injuries	8/11	7/9	NS
ISS > 20/≤ 20	6/5	7/2	NS
ATI ≥ 24/< 24	8/3	7/2	NS
Blood (1st 24 hr)	15.3 ± 3.8 units	11.6 ± 3.5 units	NS
Blood (total)	20.6 ± 4.0 units	20.6 ± 7.6 units	NS
Bilirubin maximum	2.3 ± 0.8 mg/dL	4.6 ± 1.8 mg/dL	NS
Length of stay	36.6 ± 9.4 days	28.7 ± 9.3 days	NS
Days on nutrition	12.4 ± 1.6	12.2 ± 1.7	NS
Colon injuries	7/11	4/9	NS
Pancreatic injuries	3/11	4/9	NS
Liver injuries	4/11	8/9	<0.03
Septic morbidity			
Pneumonia	2/11	5/9	NS
Intra-abdominal abscess	1/11	3/9	NS
Empyema	0/11	2/9	NS
Pneumonia or abscess (intra-abdominal or empyema)	3/11	7/9	0.07
Infections/patient	0.4 ± 0.2	1.2 ± 0.3	0.03
Infections/infected patient	1.0 ± 0	1.6 ± 3.0	<0.01

ENT, enteral; TPN, total parenteral nutrition; ATI, abdominal trauma index; ISS, injury severity score.

one TPN), or required reoperation within the first 72 hours (n = 8; six ENT, two TPN). Although there were no significant differences in blood requirements, length of stay, days on nutrition, maximum bilirubin, or individual infections between the two groups (Table 7), three of 11 ENT patients developed either a pneumonia, IAA, or EMP, *versus* seven of nine TPN patients; this almost reached statistical significance (p = 0.07) for this small group of patients. Patients receiving TPN experienced significantly more infections per patient and infections per infected patient.

Enteral feeding was not risk free, and several complications were directly related to this route. One patient in the ENT group required reoperation because of a small bowel obstruction at the jejunostomy site. This complication was totally preventable and was caused by inappropriate suturing of the jejunostomy up to the anterior abdominal wall so that the jejunal loop was reversed, causing a closed loop obstruction. Significantly more patients developed diarrhea with ENT feeding than with TPN feeding (11/51 *versus* 7/45, p < 0.01).

Discussion

The ideal clinical study randomly assigns a homogeneous population of patients to various treatment arms with prospective evaluation of outcome, excluding a few patients from the final data analysis. Although trauma patients cannot be considered a homogeneous population, they have in common a hypermetabolic response to injury, acute deterioration in lean body mass, and a high rate of septic complications. In the present study, whether septic morbidity is defined as pneumonia, IAA, or EMP, ENT feeding improved the clinical outcome of multiply injured patients.

We believe that the current prospective study provides conclusive evidence of the beneficial effect of ENT feeding in injured patients. Only two patients enrolled in the study were subsequently excluded from analysis because of early deaths. The randomized prospective methodology produced groups comparable in age, severity of injury, mechanism of injury, and blood transfusions. One can argue that the ENT population was, in fact, the slightly more injured group. Enteral patients had a higher percentage of colon, pancreatic, and blunt injuries, as well as a greater number of patients with ISS > 20 and ATI > 24 or both. Despite this, the ENT population experienced significantly less septic morbidity, including fewer infections per patient and significantly fewer infections per infected patients. Only three of 15 ENT patients sustained multiple infections, whereas 14 of 45 TPN patients had two or more infections. Most of these septic processes were either pneumonia or abscess (EMP or IAA). Neither EMP nor pneumonia could be explained on the basis of chest tube placement because 19 of 51 ENT and 14 of 45 TPN patients had chest tubes inserted soon after admission. Empyemas developed in only four of the 14 TPN patients and none of the ENT patients with chest tubes, whereas pneumonias developed ipsilateral to the chest tube in four of the TPN group and two of the ENT group. Line sepsis was a significant problem, particularly in the TPN group, probably because of the prolonged insertion, because central lines in ENT patients were removed as soon as possible. All central catheters at our institution are multiple lumen, and previous work[14,15] demonstrated a 20% sepsis rate when TPN is administered through multiple-lumen catheters. Line sepsis had a minor impact on the ultimate rate of septic morbidity; five of six patients with line sepsis in the TPN group had a simultaneous pneumonia or abscess during the course of the study.

There were no significant differences in length of stay, number of antibiotics, number of days on antibiotics, or ventilator days. One might expect shorter hospital stays and fewer antibiotic needs in the less infected ENT population. Some of this may be related to the high incidence of blunt injuries in the ENT population, which prolonged hospital stays because of associated orthopedic and neurosurgical injuries requiring prolonged bed rest, skeletal traction, or delays in placement. Antibiotic days or number of antibiotics were not different between the two groups because of prophylactic administration for open fractures, orthopedic and neurosurgical invasive procedures, and invasive intracranial monitoring. Because of the high incidence of prophylactic antibiotic coverage in noninfected individuals, no significant differences could be ascertained.

"When the gut works, use it" is a commonly expressed dictum, but clinicians are often dissuaded by the difficulties involved in providing ENT nutrition or the extra minutes necessary at the operating table to gain ENT access. Particularly in the intensive care unit population, it is easier to infuse nutrition through existing indwelling central lines than to deal with diarrhea, bloating, and frequent interruptions in feeding. This is reflected in significantly less nutrients administered per kilogram body weight during the course of the study in the ENT population, although ultimate maximal rates were similar between the two groups. It appeared it was not merely the amount of nutrition or NPC administered to the patient, but more importantly, the route through which the nutrition was administered. Identical formulas cannot be given I.V. and enterally because the human GI tract cannot tolerate the hyperosmolar load found in TPN solution. Although some difference in amino acid profiles may exist between the two solutions, similar amounts of protein, carbohydrate, and fat were administered to both groups. Enteral and TPN feeding of identical solutions has been tolerated in animal models, and the beneficial effects of gut processing of nutrients in a population prone to septic morbidity seems well supported by both laboratory and clinical experience.

Although the explanations for beneficial effects of ENT nutrition are elusive, the first clue that ENT feeding might be important in the response to and recovery from infectious challenges appeared in a series of experiments from Sheldon's laboratory, using a model of septic adjuvant peritonitis. Peterson, Sheldon, and Carpenter[16] noted increased mortality rate with protein-calorie malnutrition as well as with I.V. feeding. In subsequent experiments,[8,9] Kudsk et al. noted that both malnourished and well-nourished animals pair fed identical nutrient solutions enterally and parenterally survived the septic peritonitis better when nutrients were given through the GI tract. At approximately the same time, Alexander et al.[17] demonstrated that burned children randomized to receive a normal protein or high protein ENT diet sustained fewer septic episodes and a lower mortality rate when receiving more ENT protein. Border et al.[18] also correlated a reduced rate of sepsis with increased ENT delivery of protein. Moore et al. studied trauma patients randomized to early postinjury ENT nutrition compared with delayed[10] or immediate[11] I.V. nutrition support and also noted a higher incidence of IAA[10] or pneumonia[11] in the TPN group. A blunted acute phase protein response and higher levels of constitutive proteins also occurred during ENT feeding.[7] In a meta-analysis of several smaller, randomized prospective studies of ENT *versus* TPN feeding, Moore et al.[19] found that blunt trauma patients fed enterally experienced the most significant reduction in septic complications, a finding consistent with our data, although, in addition, our study demonstrated a lower incidence of septic complications after penetrating trauma.

To understand potential mechanisms, laboratory studies have focused on changes in mucosal structure, permeability to bacteria and toxins, gut immunology, and bacterial colonization. In rats, starvation[20] and I.V. feeding[4,21] produce dramatic histologic changes, primarily in the proximal intestinal mucosa, with loss of villus height, cellular proliferation, mucosal protein, and overall mucosal mass. Mucosal permeability to macromolecular markers increases with I.V. feedings[22] and starvation.[23] The gut mucosa, however, remains an effective barrier to intraluminal bacteria after starvation unless an inflammatory stimulus is simultaneously administered.[24] A small amount of ENT feeding quickly reverses this barrier defect.[25] The gut barrier is permeable to bacteria with I.V. TPN[6] unless the I.V. nutrition is supplemented with a specific gut fuel, glutamine.[26] Glutamine attenuates mucosal atrophy in TPN rats, although the mucosal thickness is still significantly less than that achieved with normal ENT nutrition.[27] Because glutamine released by skeletal muscle increases significantly with stress and sepsis, Wilmore et al.[28] postulated this as an endogenous protective mechanism to support the fasted gut.

Route of nutrient administration affects GI immunologic barriers. Parenteral feeding decreases biliary concentrations of secretory immunoglobulin A, with recovery occurring in animals fed enterally[29] but not in those fed parenterally, unless the I.V. TPN was supplemented with glutamine.[26] Others have noted that depressed *in vivo* lymphocyte responses after femur fracture in rats recovers with ENT but not with I.V. feeding.[30]

Despite the proliferation of laboratory data, changes in GI tract integrity to bacteria has not been proven in clinical experience. Although mesenteric lymph nodes do contain viable bacteria after bowel obstruction,[31] and gut permeability to lactulose and mannitol measured by urinary excretion increases after acute[32] and chronic[33] burns, Moore and colleagues[34] could not demonstrate bacterial translocation in the portal vein of trauma patients in whom portal vein catheters had been inserted for sequential blood sampling. This may be a problem of sampling site because translocation primarily occurs through the lymphactics, which could allow bacteria to pass through the thoracic duct and be cleared by the pulmonary vasculature, resulting in an increase in pneumonias; no data currently exist that test this hypothesis. Positive blood cultures occur after hemorrhagic shock, but there is poor correlation with the subsequent development of septic complications.[35]

Enteral nutrition is not without risk, and complications ranging from abdominal distension[36,37] to frank necrosis[38] have been reported, In the current study, patients received fewer calories through the GI tract and developed more diarrhea, documenting the difficulty in providing an "ideal" amount of ENT nutrition. In addition, one patient required re-exploration when the jejunostomy had been constructed, folding the small bowel back on itself and causing a closed loop obstruction.

The cause of increased infection in our TPN group is multifactorial, and we can only speculate that ENT feeding improves the status of the gut immune system, restores normal gut architecture and microflora, and aids the mucosa in withstanding challenges to these systems. It is unclear, in fact, whether ENT feeding improves the rate of septic morbidity or whether TPN itself causes an increase in septic complications. In the recent Veterans Administration cooperative study[39] of malnourished patients randomized to perioperative nutrition *versus* early surgery, a significant increase in septic complications, including pneumonia and line sepsis, occurred in patients with a mild or moderate malnourished state who were randomized to perioperative TPN. Müller et al.,[40] in a randomized prospective study of perioperative nutrition in patients with cancer, dropped a third arm of therapy in which patients received TPN with 50% of NPC as I.V. fat because of an unusually high rate of septic complications. These studies suggest that I.V. feeding may increase susceptibility to the development of infection.

Although the explanation is unknown, there appears to be little doubt that ENT processing of nutrients provides some beneficial effect when compared with TPN, at least in the more severely injured (ATI ≥ 24 or ISS > 20) patients. Many of the less injured patients would have recovered with no complications even without nutrition support. Because of strong sentiment for some nutrition in our patient population, we could not justify randomization to a nonfed group in this protocol. This may or may not be defensible, particularly in patients with an ATI ≤ 24 or ISS < 20. Further protocols investigating mechanisms might be limited to only those patients with more severe injuries.

In summary, it is as yet unresolved whether ENT feedings make things better, parenteral feedings make things worse, or both, but clinicians should not ignore ENT access at the initial operation and feeding because the price paid is an increase in septic complications. Whether no nutrition produces results superior to TPN, or equal or superior to ENT feeding, is unknown. Mechanisms have yet to be defined, but the principles appear to be well supported: obtain ENT access at the time of surgery to assure an opportunity for ENT delivery of nutrients, particularly in the most severely injured patients.

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DISCUSSION

DR. J. DAVID RICHARDSON (Louisville, Kentucky): Drs. Bland and Jones, I apologize for rising again. I think it is an excellent study that Drs. Kudsk and Fabian and their associates have done. When Ken asked me to discuss it, I told him that he should know I was basically skeptical of this whole concept and that perhaps it might be better to get somebody else. And he said, "Well, it might be good to have at least one skeptic." I have read the paper, and I think one cannot help but be intrigued by what certainly looks like a very strong association toward decreased infections with enteral feeding, or at least the converse of increased infections with total parenteral nutrition (TPN). Such data would support other papers on the subject, such as that by Moore and Moore from Denver, and would fit nicely into the experimental work, I guess, on bacterial translocation if one is inclined to believe in that entity. Dr. Neal Garrison of our institution has done some superb work in his laboratory in which he has shown that enteral feeding increases mucosal blood flow and, therefore, increases hepatic blood flow. Certainly, that would have theoretical benefits in dealing with patients who have the potential for sepsis.

I do believe, however, that we must analyze these data very carefully before we accept the premise that every patient with a potential major injury should have a jejunostomy tube put in at the time of initial operation. There are a lot of things that do not make sense to me from my experience in taking care of patients who are fed by a variety of methods; I cannot clinically ever tell the difference in who is going to have infection and who is not. I guess I am not convinced that there are sufficient data with most trauma patients to say that we can really prove that any nutritional support is really necessary. If one looks at the pneumonia problem, in the manuscript, the authors say that they dealt with the problem of the confusing chest x-ray by eliminating patients who had pulmonary contusion and atelectasis. Quite simply, I do not understand how you do that. Every day when I look at patients who have fuzzy-looking chest x-rays, I do not know whether they have contusion, fluid overload, or pneumonia. At the patient's bedside, determining who has pneumonia and who does not is an extraordinarily hard call. If you change two patients either way, 14 *versus* 6, you get an NS there instead of a 0.02, and you did not get on the program.

Secondly, line sepsis was a major problem. The authors made a point, however, that clearly the patients with TPN are most likely to get line sepsis, and that seems intuitive. I think we need to think about the fact that perhaps it is the line sepsis inducing other infectious problems. Patients who, once they develop a line sepsis, seem to then develop other surgical types of infection.

Thirdly, I just wonder why enteral feedings would decrease the incidence of empyema or fascitis? Even if one believes in bacterial translocation and believes that increased mucosal blood flow is important, why would that make the incidence of fascitis and empyema different? It would seem to me that a much more logical explanation would be the inclusion of a few critically injured patients in one group *versus* another — and this is a small series of patients — or the fact that one chest tube maybe did not drain the hemothorax quite as well. I would be much more likely just to tote those things up to the vagaries of clinical practice that we all see in taking care of seriously injured patients. In that most severely injured group of patients, which this study does rightly address, I think the authors noted an 11-fold difference in septic complications between the two groups: 3 of 20 in the enteral; 8 of 12 in the TPN. We have already talked about pneumonia and line sepsis, and again a difference of two or three in a group certainly sometimes could be introduced just by bias even, clearly an unintentional bias, would make that "no difference."

I certainly commend the authors on what I think is a good paper, one that fits well with other reports in the literature. But based on clinical experience, I still am not ready to say that every patient who has a serious injury ought to have a J-tube put in, because we clearly find significant jejunostomy complications in our unit. Small bowel obstruction here and there, a tube that gets pulled out of the bowel with resultant peritonitis, diarrhea commonly causing dehydration. Occasionally, in elderly patients, we have seen dead bowel as well.

Finally, neither group had an ultimate improvement in survival. The authors talked a lot about comparative costs but did not look at all factors related to cost, such as nursing time in changing the beds because of increased diarrhea or keeping the enteral feeding tubes open. These are complex issues that must be carefully evaluated. Thank you.

DR. LEWIS M. FLINT, JR. (New Orleans, Louisiana): Thank you, Dr. Bland. Based on some comments that have been made from this platform this afternoon, I feel compelled to point out that the gentleman on my far left is not Dr. Carroll Scott Conner of Jackson, Mississippi, nor is it Dr. H. William Scott of Nashville, Tennessee, but he is in fact our Secretary, Dr. R. Scott Jones. Based on what I have heard this afternoon, it seems to me the audience needs to be aware of that.

Well, on to the discussion of this study, which in my opinion emanates from one of the really first-class trauma research units in this country. I want to believe it, I honestly do, Ken. But I must say that, based on my experience, I remain skeptical. And I would like to ask a few specific questions.

First of all, you have achieved a success rate with enteral nutrition, which I do not think has been achieved in any other unit of which I am aware. Two patients of nearly 50 with a lack of tolerance of the enteral feeding is a feat that we have not been able to achieve in several years of trying. I am not sure why enteral nutrition should lower the rate of pneumonia. Perhaps it is that enteral nutrition alters the bacteriology of the intestine, which we believe is associated with the frequency of pneumonia. And I would ask, do you have any data that would look at the bacteriology of the stomach or the hypopharynx in your patients who had enteral nutrition *versus* total parenteral nutrition (TPN) to see if there was any difference there? I think you would have to acknowledge that the numbers in the groups are somewhat small to draw any specific conclusions, and perhaps the best thing that can come out of this is to stimulate a group of interested trauma investigators to do a multicenter study that would really address this problem.

We are more likely to be aggressive about the placement of the transnasal duodenal tubes for nutrition in our trauma patients, and we have found that this works pretty well and avoids the problem of having a surgically placed jejunostomy.

With regard to the jejunostomy, I would like to ask, how the tube was managed in the patients who had TPN? The ideal control would be the administration of a non-nutrient solution by the jejunostomy tube in those patients who were getting TPN. There are some data, if you once again believe the translocation studies, that simply flushing the bowel out with a solution and moving those bacteria into the bedpan, as opposed to letting them stay in the bowel, might reduce some of the morbidity that we see regarding bacterial overgrowth.

I enjoyed the paper. I think it is very provocative. I honestly believe that with a little more confirmation, you might convert Dr. Richardson and me. And I congratulate you on a fine effort.

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): Dr. Bland, Dr. Jones, Ladies and Gentlemen. Dr. Fabian, I rise not as a skeptic but as a believer, because I think this represents, if I understand you correctly, another demonstration of the importance of translocation in the bowel that does not have enteral feeding. We certainly see this in babies who are not fed initially enterally; they develop septic complications much more frequently. And interestingly enough, that appears to be the main source of their infected total parenteral nutrition lines, namely, bacteria from the gastrointestinal tract. And so I think it is not too far amiss, Dr. Richardson, Dr. Flint, that even empyemas and pneumonias might be coming through the bloodstream from the gut.

But I would like to ask you whether you have done any bacteriologic studies of the bloodstream in these patients to see if they have positive blood cultures during the period that they are developing sepsis.

Finally, it seems to me that the use of jejunostomy is aggressive. Why not use a nasogastric or a nasal duodenal tube, especially in those patients who do not require operative intervention, those who are being treated nonoperatively, particularly those with blunt trauma, which I saw in your series were approximately 25% of the patients. I do not know how many of them required operative intervention, but it would seem to me heroic to carry out a jejunostomy if that was the only reason for opening the abdomen. Why not use nasal duodenal feedings, but to achieve the same purpose, namely, to feed the gastric and duodenal and small intestinal mucosa? I would be interested in your comments. Thank you.

DR. JOSEF FISCHER (Cincinnati, Ohio): Dr. Bland, Dr. Jones. This is an interesting and provocative paper, and I rise to discuss several aspects of it, some of which are interesting particularly to me, and to ask a few questions.

First of all, Dr. Alexander did not correct the allusion to the paper that he published and presented before the American Surgical in which the operant difference between the two groups was the amount of protein. It turned out in retrospect that the group that had 25% protein instead of 15% protein got slightly more of their nutrition enterally than parenterally, and this led to, I think, his work on translocation.

It is interesting to me that we have done a large number of studies in enteral and total parenteral nutrition (TPN) and have never really detected any major difference in outcome regardless of the site of the study or nitrogen balance. The hypothesis that one is better or the other was worse would probably be better restated that most physicians and surgeons interested in nutritional support would suggest that if you can nourish a patient using the gastrointestinal tract, you do so, and only under carefully controlled circumstances when you fail to have the gastrointestinal tract operant is parenteral nutrition indicated.

Now it is interesting that there are two areas in which you saw the difference in increased sepsis: one was liver injury, and the other was pancreas injury. Tom Goodgame, when I was still in Boston, and Harry Sax in Cincinnati, each independently studied early parenteral nutrition of patients with pancreatitis. In both studies there was an early increased incidence of line sepsis and other infections, specifically in patients with pancreatitis, only in patients with pancreatitis, at a time when the general line sepsis rate was running about 1.8%. There may be something specific about injuries to the pancreas and pancreatitis and TPN. Mike Nussbaum of our laboratory has attributed this to prostaglandin E_2 activation and suppression of immunologic function. This appears to occur only within the first week, and then it seems to subside. There may be something in those particular data.

I am a little troubled with the horrendous incidence of line sepsis. To my calculation, it is someplace between 13% and 16%. This is excessive in any unit under any circumstances. And so I wonder whether or not one of the operant mechanisms here is whether or not these patients get sick with line sepsis, very much as David Richardson suggested, and then as the line sepsis goes on, they then become prey to other nosocomial infections. And I would like to ask you, what do you think is the average time in which lines were infected before detection and pulling of the line? In a patient who is severely injured, in an intensive carte unit in which the source of infection may not be obvious, line sepsis can smolder for a number of days, during which time the patient's condition may deteriorate.

And I also would like to ask about Alex Haller's questions about what infections were in the lines. Third, just a comment on diarrhea. I notice your diarrhea incidence was about 22%. And I do not know whether you consider that a complication. But with severe diarrhea of tube feedings in our own situation when we have tried to do comparative studies between enteral and parenteral nutrition, we have had some very serious complications in patients with enteral nutrition. So I would just close by saying that I think the two measures of nutritional support are complementary. I do not think there is one way of doing it; they each have their problems. But I do think that when you do TPN, a line sepsis rate of about 13% really needs to be examined very carefully. Thank you very much.

DR. KENNETH A. KUDSK (Closing discussion): I want to thank everybody for their kind comments. I also have had a lot of questions about things like bacterial translocation and bacteria coming from the gastrointestinal (GI) tract when we do not feed our critically ill patients.

The question has come up about giving no nutrition to some of these patients. We talked about this at some length before entering into the protocol. There have been other people that have tried to do this and to get a control group with no nutrition. We did not believe that that was ethically correct. But after looking particularly at the populations of patients who had the low injury severity score and the low abdominal trauma index, that may not be appropriate. But that is why we thought that all patients should be randomized. And just as Dr. Moore was criticized for delaying intravenous (IV) nutrition in his first study, we believed we needed to start both therapies simultaneously.

The question has come up about pneumonia and sepsis. And diagnosing pneumonia can be very, very difficult, as all of you know. In most patients, it is really pretty obvious. You see someone who has a socked-in left lower lobe, you perform a bronchoscopy, and you find pure pus there, and they have a fever, a leukocytosis, and respond to antibiotics, there clearly is no doubt that that patient had pneumonia. And 80% of the patients in this study were very easy to diagnose. The other 20%, however, were very difficult. These cases were reviewed by physicians who were blinded to therapy. X-rays were sometimes reviewed, and the chart was reviewed in terms of response to antibiotics without those physicians knowing which group they were in, and the decision was made as to whether they were infected or not, and we lived with that diagnosis. I do not know any other way in which we could have handled that problem.

The question has come up from a number of authors about the line sepsis and whether line sepsis perhaps was causing the pneumonia. You have to realize that only 50% of people who developed subsequent pneumonias had had a line sepsis. We watched the lines very carefully; they were changed every 3 days over a guidewire, and sent for culture. And so it is unlikely that there were long periods that these people could have been continually seeding their lungs or other organs from an infected line.

I do not think that there is any effect, Dr. Richardson, on either necrotizing fasciitis or on empyema. In fact, there was no significant difference in fasciitis between groups. If you look at the data very closely, the empyemas that developed were for the most part associated with the development of a pneumonia. There was one patient in the enteral group and two people in the parenteral group who developed empyemas but did not have a simultaneous pneumonia, so I suspect it is just a more virulent process. And in fact if you look at empyemas, there was only one patient who did not have a simultaneous pneumonia or an intra-abdominal abscess who had an empyema. In regard to pneumonia and the number of infections and how close we are to statistical significance, two patients here or there, we were also statistically significant with abscesses—intra-abdominal and intrathoracic. Very significant. Pus is pus. And I think that there is an effect of nutrient administration that we cannot ignore.

Dr. Flint, you commented on the success that we had had with enteral nutrition. My colleague, Dr. Brown, had published a number of years ago that if you have a member of your service who really wants to make enteral nutrition work, you can make it work. And I think that because we had the cooperation of the nutrition support service, together with me making rounds the majority of the days on these patients, that we were able to work through problems. If one thinks that nutrition support through the gut is unsuccessful if you do not get up to 1.5 g protein and 30 kcal/kg, essentially 100 percent of what their needs are, enteral feeding is almost always going to be unsuccessful in most patients. Fifty per cent of patients tolerate it without any problems. Now, in 10% of patients you have a lot of problems, but it is the other 40% that you need to play with, cut their rate down, go up with it; I think that is reflected in the fact that the total amount of nutrition given to the enteral group was significantly less during the course of the experiment. But if you looked at the maximal rates that these people received, they were very comparable. It took us longer to get to the maximal rate with the enteral group. But still it is a matter of working with it, and I am satisfied if I can get two thirds of the calculated requirements, through the GI tract. If that is as high as I can go, I will be satisfied with that, and I do not give intravenous nutrition. The cutoff for failure to tolerate as defined in the manuscript was if they were not receiving at least 50% of their calculated rate within 7 days, they were considered a failure. A lot of these patients received 65% to 85% of their energy requirements.

A point was brought up by Dr. Flint about the lower rate of pneumonia and perhaps feeding with a nasoenteric or nasoduodenal tube. That also was brought out by Dr. Haller. This may be very site specific. We have the sucralfate study, which is being analyzed, in which it appears that if we try to deliver the nutrition into the stomach, that there appears to be a higher rate of infection. This seems to be critical, that you deliver the nutrients beyond the ligament of Treitz. And I think any one of us who have tried to do nasoduodenal feedings know that within a day or 2 those things often flip back into the stomach, and if we have made a serious commitment to taking a nasoduodenal tube and getting it beyond the pylorus, we are talking about repeated endoscopies on these patients to get it into that anatomic position.

So I think the principle here is that we have an opportunity at the operating table to get access to the GI tract; that is the time we need to cannulate the GI tract because we cannot depend on nasoenteric tubes.

How did we manage the jejunostomy tubes that were not being fed? They were just flushed with normal saline three times a day. After the first 40 patients, once they developed infections, then we switched them over to immediate enteral feeding. We considered them a failed TPN patient.

I have commented on the line sepsis. Except to say that line sepsis in an intensive care unit (ICU) population that had multiple-lumen catheters is associated with a much higher rate of sepsis than use in a patient who has an inviolate line for TPN.

There were two studies that Dr. Fabri and I performed when we were at Ohio State in which we randomized patients to two single-lumen catheters *versus* a double-lumen catheter or a triple-lumen catheter *versus* two single-lumen catheters. And in those situations, the rate of sepsis in the ICU population was about 20%. I think what this reflects is the kind of patients that we are dealing with in the ICU, manipulation of those lines and the chance of them getting infected increases. By and large the lines were infected with *Staphylococcus* sp. The bacteriology that we obtained from the pneumonias were very characteristic of the typical pneumonia: *Enterobacter* or *Aerobacter* aerogenes, some *Pseudomonas*, and a lot of *Staphylococcus* in our institution.

As for the question about diarrhea, it is a significant problem. It occurred in 25% to 30% of the patients. We have solved that problem now. We use a fiber-containing diet, which you can give by needle catheter jejunostomy, and have really cut down on the incidence of diarrhea using that. Definition is important — if someone has a semiformed stool, that's not diarrhea, even if it's five or six times a day. Diarrhea that caused a continuously wet bottom needed therapy to avoid breakdown of skin. What we did is we cut back on the rate of nutrient administration, down to 75 mL/hour, and managed them with that amount. I think that answers most of the questions.

I would particularly like to Dr. Fabian for his excellent presentation, and my colleagues Dr. Minard and Dr. Croce for recruiting patients into the protocol. I would like to thank the Association for allowing me to present the data. I am really sorry that Dr. Sheldon was not here today. He is the gentleman who, 12 years ago when I was in his laboratory, gave me an opportunity, as we talked about earlier in the study, to look at enteral *versus* parenteral feeding. And he really is the one who first introduced this topic and suggested that potentially there is a benefit that our patients get when we deliver nutrients through the gut that we do not get when we feed these patients intravenously. And I am sorry he was not here to hear this study today. Thank you very much.

Carotid Endarterectomy Monitored With Transcranial Doppler

HOLT A. McDOWELL, JR., M.D., GARY M. GROSS, M.D., and JAMES H. HALSEY, M.D.

Intraoperative transcranial Doppler monitoring of cerebral ischemia during carotid clamping under general anesthesia was done in 238 carotid artery operations, mostly endarterectomy. Depending on the severity of reduction of middle cerebral artery mean velocity, patients were classified as no, mild, or severe ischemia at clamping. With a carotid shunt, velocity was always in the "no ischemia" category during shunting. For patients with no ischemia, stroke was significantly lower without a shunt (2/175 no shunt *versus* 2/12 shunt). For mild ischemia, shunting did not affect the stroke rate (1/20 no shunt *versus* 0/9 shunt). For severe ischemia, strokes were less frequent with a shunt (4/9 no shunt *versus* 0/13 shunt). Intraoperative electroencephalogram predicted most, but not all severely ischemic cases. Carotid back pressure correlated with Doppler velocity, but transcranial Doppler was more helpful. Transcranial Doppler is a new and valuable technique in carotid surgery.

CAROTID ENDARTERECTOMY HAS proven value in prevention of stroke in some groups of patients with atherosclerotic plaque of the intracervical carotid artery. Perioperative stroke has been reported to occur in 1% to 21% of cases, depending on the center and indications for surgery.[1,2] Some authors declare that some of these strokes are due to cerebral ischemia during the time of temporary carotid artery occlusion for the endarterectomy, but others ascribe perioperative stroke to embolism of plaque or thrombus during the exposure of the artery, and after reflow. The purpose of this study is to determine whether transcranial Doppler assessment of intracranial blood flow during carotid endarterectomy allows effective detection of cerebral events resulting in stroke, and whether this information can reduce the risk of stroke.

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Methods

Patients undergoing carotid surgery requiring clamping of the carotid artery underwent monitoring of transcranial Doppler (TCD) velocity in the middle cerebral artery (MCA) during surgery. A total of 238 operations at University of Alabama at Birmingham Medical Center and Birmingham Veterans Administration Hospital were monitored. Two hundred thirty-one of the procedures were carotid endarterectomies, but seven had other carotid artery procedures requiring similar clamping for a similar time interval, including four carotid-subclavian bypasses and two carotid artery resections with replacement for tumor or tortuosity, and are included in this series. Of the patients considered for this study, an additional 26 operative procedures are not reported, because before operation a good MCA signal could not be obtained, usually because of temporal bone thickness.

Mean age was 66 years (±9). Seventy-six per cent were male. Twenty-one patients had staged bilateral carotid endarterectomy, reported here as two separate operations. The indication for endarterectomy surgery was asymptomatic severe stenosis (greater than 80% area narrowing) in 27%, and symptomatic stenosis (previous transient ischemic attack or stroke) in 73%. Four patients had a fixed stroke before operation. No patient had stroke in evolution as an indication for surgery.

All operations were done with general anesthesia using nitrous oxide and isoflurane. A radial artery cannula was used for monitoring of systemic blood pressure. Many patients had preoperative oral antiplatelet agents. During the operation, heparin, 75 to 100 U/kg, was given before clamping. Sometimes, an additional dose of 1000 to 2000

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units was given if clamp time exceeded 30 minutes. Average clamp time was 23 minutes (range, 5 to 87).

Most operations were monitored with 10-lead electroencephalogram (EEG), and intraoperative continuous assessment of all channels by an EEG technologist with supervision by a neurologist. In many cases, intraoperative digital subtraction angiography was done before closing the incision, to assess the technical result. Most appeared satisfactory, but in two cases, the artery was re-explored for a technical defect, one at the internal carotid endpoint, the other for an occluded external carotid artery, which was corrected by a limited endarterectomy through an external carotid arteriotomy. Patches were used at the discretion of the surgeon, with no consistent policy among the five surgeons. One surgeon routinely patched all carotid arteries with Dacron, another selectively patched some with saphenous vein if a smaller than normal internal carotid had been incised, another selectively used polytetrafluoroethylene patches, and another never used a patch.

Decision on use of a shunt depended on the choice of the surgeon, and generally reflected the controversies in this field in the larger community of all carotid surgeons. Some of the surgeons never shunted, but another used a shunt for EEG changes. One surgeon routinely used a shunt in nearly all carotid operations. In the first years of the study, the relevance of low TCD velocity was unproven, so TCD data were not used in determining whether to insert a shunt, but in more recent times, with assessment of the data, more patients with TCD ischemia have had shunting. For this study, shunting is defined as insertion of a temporary internal carotid artery shunt with <4 minutes' total ischemic time during the operation.

Transcranial Doppler was monitored with an EME TC 2–64 (Eden Medical Electroniks, Uberlingen, Germany) or Medasonics (Medasonics Corp., Fremont, CA) instrument, as we have previously described.[3] This is a range gated pulsed wave Doppler with 2-MHz transducer at power of 1000 mW/cm^2. The transducer is secured to the scalp with adhesive dressings, and protected from motion with a plastic housing. The pulsed system allows selection of the depth of measurement, with the MCA in this series located at a mean depth of 48 mm (range, 35 to 55).

At the discretion of the surgeon, some patients also had measurement of carotid stump pressure. After heparinization, this was done with an 18-gauge, 1-inch needle in the common carotid artery. If the bifurcation stenosis was nearly totally occlusive, then the stump pressure catheter was inserted directly into the internal carotid artery.

All patients had complete neurologic examination on awakening, then periodically during the hospitalization. For this study, patients who had a neurologic deficit persisting for over 24 hours after the surgery are classified as having sustained a stroke.

Results

Three patients died within 30 days after surgery, for a mortality incidence of 1.3%. Two deaths were consequent to stroke; one was due to myocardial infarction. Nine strokes occurred, two in the shunted group of 34 patients (5.8%), and seven in the 204 patients without a shunt (3.4%, p = nonsignificant).

In Figures 1 and 2 are representative TCD tracings during operative procedures. In those cases with severe depression of the MCA velocity after clamping, a large increase in velocity was noted if a shunt was inserted. For unshunted patients in the group of patients classified as severe ischemia after clamping, average mean velocity at clamping was 2% of baseline (±4%). In shunted cases with severe ischemia at clamping, mean velocity averaged 3% (±5%) at clamping, and 76% (±22%) after insertion of a shunt. In all cases where a carotid shunt was inserted, the mean velocity during shunting was in the "no ischemia" category (>41% of baseline), no matter whether the preshunt velocity indicated no ischemia, mild ischemia, or severe ischemia.

One hundred eighty-seven cases (Table 1) were classified as having no ischemia during clamping (mean velocity > 41% of baseline). Of these, 12 were shunted, one of whom suffered a stroke, evident on awakening, and another developed severe disability 2 hours after awakening from anesthesia that on re-exploration was found to be due to platelet thrombosis of the carotid artery. A mild EEG change had occurred in this case at clamping. The stroke rate for shunted cases with no Doppler ischemia was 17%. One hundred seventy-five had no shunt, of whom 1.1% sustained perioperative stroke, both due to cerebral hemorrhage. One of these had hyperemia by in-

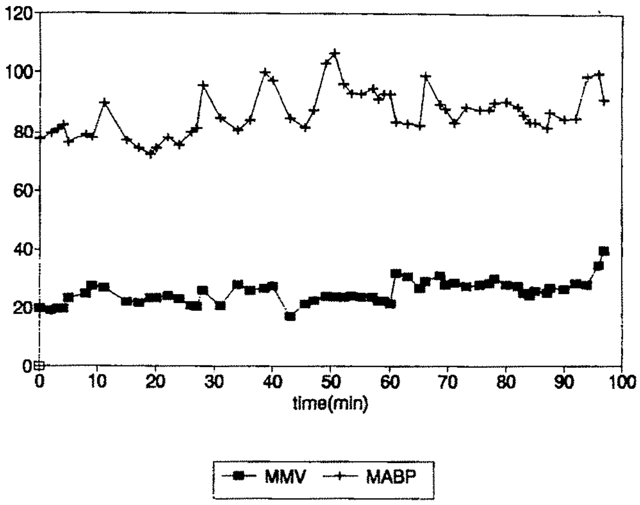

FIG. 1. Carotid endarterectomy. Shunt not used. Artery clamped at 40 min, resulting in no ischemia (MMV > 41% of preclamp level).

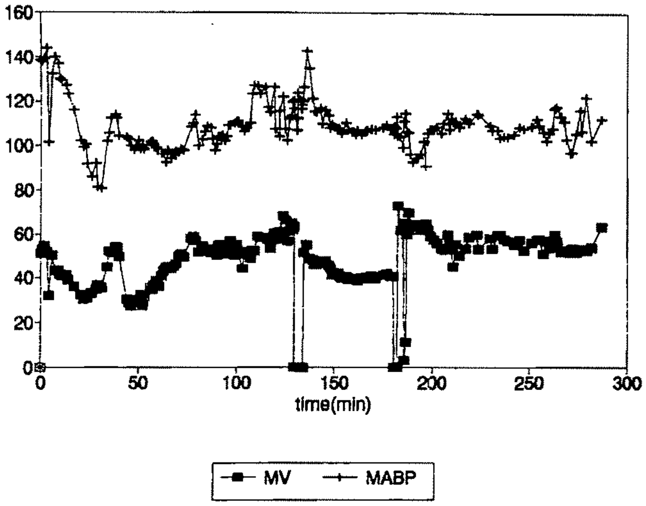

FIG. 2. MCA Doppler velocity (MV). Severe ischemia at clamping time (130 min on X-axis), relieved by shunt. Ischemia again at 180 min when shunt is removed. Patient had severe EEG changes coincident with the times when MV = 0. MABP, arterial systemic mean pressure.

tracranial Doppler in the operating room, the other had hemorrhage on the fifth postoperative day. In procedures with no ischemia by intracranial Doppler, the lower stroke rate when a shunt was not used is statistically significant to $p < 0.022$.

Twenty-nine cases were classified as mild ischemia. Nine were shunted with no strokes, and 20 were not shunted, with stroke in one case (5%), due probably to spontaneous occlusion of the stenotic carotid artery before clamping, early in the anesthetic course, with unrecognized EEG changes.

Twenty-two cases were classified as having severe ischemia at clamping (mean velocity < 15%). Thirteen were shunted, with no strokes. Nine were not shunted (including one case where a shunt was actually inserted, but a very high ischemic time of 6.5 minutes with MCA flow of zero still occurred because of technical difficulties of the operation). In the unshunted category, there were four strokes, for an incidence of 44% ($p < 0.0173$ for shunt compared with no shunt).

TABLE 1. *Rate of Perioperative Stroke*

Ischemia	V	Shunt Status No.	Stroke No. (%)
None	>41%	Shunt 12	2/12 (17)
$p < 0.03$		No shunt 175	2/175 (1.1)
Mild	16–40%	Shunt 9	0/9 (0)
p = NS		No shunt 20	1/20 (5)
Severe	0–15%	Shunt 13	0/13 (0)
$p < 0.02$		No shunt 9	4/9 (44)

Fisher's exact test.

Electroencephalogram was not recorded in 13 cases, and in two additional cases the EEG was suppressed by deep anesthesia with supplemental barbiturate at the time of clamping to the level of suppression burst anesthesia. In 181 procedures, there was no change in EEG at the time of clamping. For these, the mean velocity averaged 70% of the immediate preclamp level ±24%. For the 28 cases with mild EEG changes, mean velocity (MV) was 51% ± 30%, and for 22 with severe EEG change, 10% ± 13%. Five cases had severe ischemia by intracranial Doppler, but no abnormality of the EEG. Two of these had strokes. Neither was shunted.

Transcranial Doppler velocity during the period of carotid clamping generally increased mildly during the first 5 minutes of occlusion (Fig. 3), but after this did not vary by much. For the unshunted cases, there was no correlation of clamp time with severity of Doppler ischemia, or with occurrence of stroke.

Of the 22 cases of severe ischemia at clamping of the carotid, the EEG did not change in five. Two of these had persisting neurologic complications. One was mild; one was severe and ultimately fatal. In neither of these was a shunt used. In patients sustaining perioperative stroke, TCD still returned essentially to baseline levels at the end of the clamp time. This suggests that the strokes were ischemic in origin, rather than embolic, where a persistent low velocity would be expected.

There was a positive correlation of TCD velocity after clamping and absolute carotid back pressure (Fig. 4). All cases with severe ischemia by TCD had stump pressure below 40 mmHg. Many unshunted cases with low stump pressure, however, had resolution of the severe TCD ischemia within 5 minutes after clamping (Fig. 3).

On preoperative arteriogram, 33 cases had contralateral carotid occlusion. Of these, 14 had no ischemia by TCD

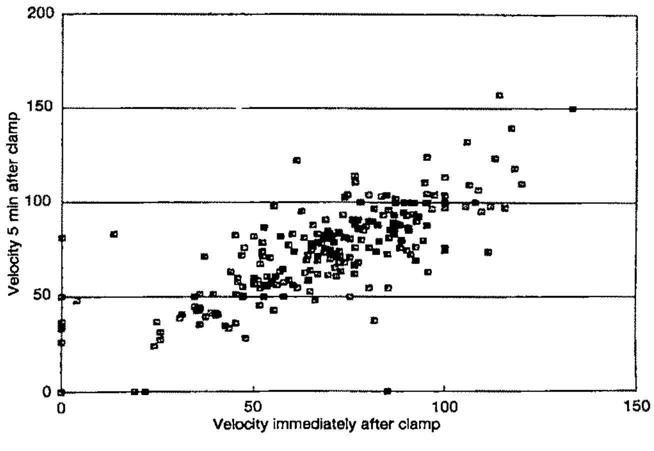

FIG. 3. Velocity immediately after clamping correlates with velocity 5 min later, but some cases with zero flow spontaneously increased to no ischemia without a shunt.

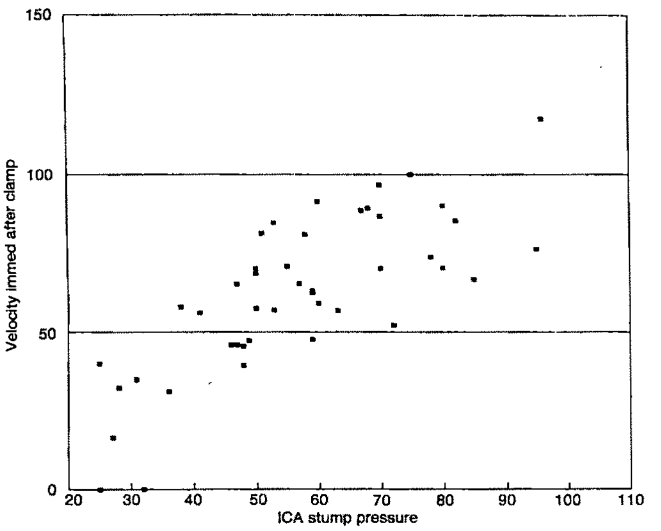

FIG. 4. MCA mean velocity as percentage of preclamp level. Lower stump pressure correlates with lower mean velocity after clamping.

on clamping. Eight had mild ischemia, and there were 11 with severe ischemia. Severe ischemia was therefore more likely if the contralateral carotid artery was occluded. There was no correlation of nonocclusive contralateral stenosis with TCD results.

Transcranial Doppler had value in management of other complications. Sometimes hyperperfusion was noted, occasionally followed by cerebral hemorrhage. Five per cent of procedures had mean velocity after declamping greater than twice the preclamp level. One of these sustained cerebral hemorrhage. Also, a case of intraoperative, postendarterectomy intimal flap, obstructing flow and requiring revision of the endarterectomy, was noticed by TCD, but was not seen on digital subtraction angiography.

Mean preclamp systemic blood pressure in the nonischemic category was 97 ± 17. For mild ischemia, pressure was 98 ± 15, and for severe ischemia, 101 ± 16.

Discussion

Transcranial Doppler velocity assessment of flow in the MCA can potentially predict cerebral ischemia during carotid surgery. Recent technical refinements have allowed accurate insonation of the MCA in most subjects.

Insertion of a plastic shunt tube into the common and internal carotid arteries during the time of carotid bifurcation occlusion may allow temporary perfusion of the ipsilateral carotid territory. In an individual case, this might help prevent perioperative strokes related to ischemia, but could increase the incidence of strokes due to embolization, or can damage the intima of the more distal internal carotid artery.[4,5]

Some surgeons routinely use a shunt in all carotid endarterectomies. Others seldom use a shunt, but some rely on selective shunting. Selective shunting requires some assessment of which patients are at potential risk for brain ischemia during clamping. Preoperative status of the contralateral carotid, preoperative neurologic status of the patient, intraoperative back pressure measurements, local anesthesia with monitoring of neurologic examination, intraoperative measurement of regional cerebral blood flow with xenon, and intraoperative EEG have all been used to make this decision, but there has been inconsistent value to these modalities in preventing operative stroke. For example, Sundt[6] reported a 24% incidence of major focal EEG changes during carotid clamping, which is then an indication for use of a shunt. But in other series that do not use EEG or shunts, the incidence of operative stroke is much lower than 24%. In cases monitored under local anesthesia, 3% have serious cerebral dysfunction despite a normal EEG, and 5.1% have an abnormal EEG despite a normal neurologic examination. A persistent regional cerebral flow below 10 mL/minute with xenon is associated with irreversible neuronal damage, but our own work did not show low xenon flow to be a good predictor in carotid endarterectomy.[7]

In this series, TCD assessment of severely reduced MCA velocity during carotid clamping accurately predicted the need for a carotid shunt. Severe ischemia, such that use of a shunt would be considered, occurred in 9.2% of cases. Thus, by TCD, more than 90% of carotid operations do not have criteria for use of a shunt. These findings help explain why those series in which shunts are always used do not have a substantially different stroke rate from centers using selective shunting, or centers never using shunts. In more than 90% of carotid operations, by these TCD data, a shunt has no value, and the data also suggest that the shunt may increase the risk of stroke in patients with adequate TCD velocity during clamping.

Patients sustaining severe ischemia by TCD were not distinguishable by any established preoperative criteria from those with mild or no ischemia. None of the severely ischemic patients had a history of fixed stroke before the surgery. Although contralateral occlusion was more common in the group with severe ischemia (50%), most patients with contralateral occlusion (2/3) did not have severe ischemia.

It could be argued that severe ischemia was present in some patients because their blood pressure was not adequately increased before or during clamping. The blood pressure data, however, argue against this hypothesis. During the period of clamping, the anesthesiologist usually maintained blood pressure about 10% above baseline levels, to facilitate cerebral perfusion. In some cases, a transient low blood pressure reduced the TCD velocity at test clamping, so clamping was delayed until the blood pressure was in an acceptable range. All TCD velocity data described above are associated with an effort at optimal management of systemic pressure. In all cases of severe ischemia at clamping, it was the general perception of the surgeon that a reasonable effort had been made to optimize the systemic arterial pressure, and that severe ischemia was truly due to inadequate collateral circulation to the ipsilateral MCA, unresponsive to reasonable efforts to increase the blood pressure, carried out with the anesthesiologist's knowledge of the response of MCA velocity to his efforts with blood pressure. This view is supported by the blood pressure data. At clamping, there was no significant difference in the mean systemic blood pressure for the severely ischemic, mildly ischemic, or nonischemic categories, and in fact there was a nonsignificant trend toward higher blood pressures in the group with severe ischemia by TCD.

Neurologic morbidity was usually, but not always, preceded by evidence of ischemia by both EEG and Doppler. Presumably, the reason that in some cases one of these monitoring techniques shows severe ischemia when the other does not is that EEG is a good test of cerebral cortical activity, but TCD is a better test of deeper portions of the hemisphere, including the basal ganglia and internal capsule.[8]

All of the patients with severe Doppler ischemia had low stump pressure, but many with adequate Doppler flow also had an initially low stump pressure. The stump pressure is an isolated measurement at one time, whereas the TCD has the advantage of continuously assessing intracerebral arterial flow, which may increase during the first few minutes after clamping.

In conclusion, TCD is our primary cerebral monitoring technique in the clinical practice of carotid surgery. We believe it is of more practical value than EEG, but we also use EEG. Transcranial Doppler can be obtained in over 90% of patients, and is not inconvenient to the surgical procedure. Severe TCD ischemia for which we recommend a shunt does not occur in most patients. Use of a shunt is associated with lower stroke incidence in severe TCD ischemia. Shunting is not associated with a lower incidence of stroke in mild TCD ischemia, so we do not recommend shunting for most carotid surgery. Measurement of back pressure does have value in assessing the tolerance of the brain to temporary carotid occlusion during carotid endarterectomy.

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DISCUSSION

DR. ROBERT B. SMITH III (Atlanta, Georgia): Dr. Ochsner, Dr. Jones, Members and Guests, Now that some of the long-awaited results of both the symptomatic and asymptomatic randomized clinical trials of carotid endarterectomy are being reported, new standards of acceptable perioperative morbidity and mortality rates are being formulated. The combined serious morbidity rates, stroke plus death, for the NASCET study and for the two VA cooperative studies recently reported range from 2.1% to 5.5%. The same value for the experience described by Dr. McDowell was 5.0%, placing them just within acceptable limits of current practice. This outcome was achieved with a mixed approach to shunting and patching, according to the preference of the individual surgeons. The only uniform element was the use of transcranial Doppler to monitor middle cerebral artery flow intraoperatively. It is interesting that transcranial Doppler flow correlated rather well with the 10-lead electroencephalogram (EEG), but less well with carotid stump pressures. At Emory, we have no experience with transcranial Doppler monitoring intraoperatively, preferring either local anesthesia, allowing constant communication with the patient, or compressed spectral array EEG if general anesthesia is used. Regardless of the method of monitoring, however, it is our preference to shunt all patients. Although we agree that probably fewer than 10% of carotid endarterectomy patients actually require shunting, an all-shunt policy avoids the search for that 10% and the possibility of an erroneous selection process. It is our view that the risks of shunt insertion are exceedingly small and are outweighed by the benefits achieved.

I have several questions for the authors. How would you advise managing a patient whose transcranial Doppler flow is already quite low before clamping but does not change appreciably with flow interruption? Should that patient be shunted or not? How much does this monitoring method add to the expense of the operative procedure, and is it more or less costly than 10-lead EEG? Do you really need both simultaneously for safe performance of the operation? Finally, you were able to detect postendarterectomy hyperperfusion in a few patients, sometimes followed by intracranial hemorrhage. Once hyperperfusion is known, are there any practical measures to minimize the likelihood of catastrophic intracranial bleeding? I enjoyed the paper. Thank you.

DR. WILLIAM EDWARDS (Nashville, Tennessee): Dr. Ochsner, Dr. Jones, Members and Guests, I enjoyed Dr. McDowell's presentation and appreciate him bringing this information to us. I must say, however, that his stroke rate struck me, as I read the abstract, and I thought that that indicated some problems in his study.

I think that we need to look at the new cooperative study showing the parameters of stroke that had occurred in that group; we need to remember that from operative intervention we are going to have a stroke rate, 1% or less, it is hoped. The natural history of stroke rate from the disease itself may be somewhere from 5% to 15%, which gives us vascular surgeons a window in which we can safely perform carotid endarterectomy. And I think, as Dr. Smith pointed out, it is incumbent on us to be certain that we can offer this operation in a milieu that is safe, with a low morbidity rate, a low stroke rate, and a low mortality rate.

In performing carotid endarterectomy, I have used general anesthesia, light general anesthesia. I do not prefer to use local, because I began with local anesthesia many years ago in Houston and decided that general anesthesia is much better. I also was taught to shunt, and there is no decision on my part as to whether to shunt or not. I shunt every case unless technically I am unable to insert a shunt. And there are very few cases in which that occurs. This also allows me to teach residents and fellows exactly how to insert the shunt safely. I have believed for a good many years that the postoperative platelet thrombosis that occurs after carotid endarterectomy was related in some way to platelet aggregation. And if we could prevent those platelets from trying to repair the injury that we as surgeons have created, then we might be able to lower that postoperative stroke rate. And by using aspirin, dipyridamole after operation, and dextran in those patients who have not received any of these, we were able to very dramatically reduce our incidence of postoperative stroke as a result of the platelet aggregation and the thrombosis.

I would like to ask Dr. McDowell two questions regarding their strokes: Exactly when did these strokes appear? Were they patients who had their neurologic deficit when they awoke from their anesthesia or were they strokes that appeared during the postoperative period? We have developed the attitude that if the patient wakes up with a neurologic deficit, we would have that patient wake up in the operating room. If they show that neurologic deficit, then we will re-explore that carotid artery to be certain there is not platelet aggregation occurring. By the same token, the patient who, during his or her first few hours of convalescence, demonstrates a hemiparesis, will be taken back to the operating room as well.

The second question is, were there technical problems with shunts? I think that learning to use a shunt will certainly minimize the technical problems, but that technical problems can be produced. Again, I appreciate him bringing the material, and appreciate the opportunity for the floor. Thank you.

DR. DENTON A. COOLEY (Houston, Texas): I have enjoyed Dr. McDowell's presentation and believe we will try this method of monitoring when it becomes available. As I have listened to the endless controversy about the management of the stenotic carotid arteries, I have been amazed at the circular nature of the discussions. I have always thought that vascular surgeons never changed their minds and seldom even rearranged their prejudices. After a large experience using the standard technique of carotid endarterectomy by longitudinal incision, about 2 years ago I reverted to using the technique that was used in the first carotid endarterectomy in 1954, that is, a transverse incision with eversion endarterectomy. This technique eliminates the need for shunts or for patches. The longitudinal incision naturally leads to stenosis and thrombosis. You never see a thrombosis in a transverse incision. The transverse eversion technique never exceeds 10 minutes of carotid occlusion, and the average is 7 to 8 minutes of carotid occlusion. I think that vascular surgeons ought to re-examine this technique of carotid endarterectomy, give up shunting and patching, and return to using transverse incision, which is a much more anatomic repair.

I would like to ask Dr. McDowell to elaborate on those patients with 100% occlusion in the contralateral carotid artery. We never used shunts in patients in whom we used longitudinal incisions, and I never saw an ischemic injury in a patient with a contralateral 100% occlusion. Can you explain that on the basis of your monitoring technique? Thank you.

DR. HOLT W. MCDOWELL, JR. (Closing discussion): Dr. Cooley, I cannot explain it. We did have marked drop or at least a higher significance of drop on contralateral occlusion, and the incidence of shunting was higher based on those data, but I cannot explain why you have never seen a stroke with a contralateral occlusion because our results would indicate that maybe contralateral occlusion would have a higher stroke rate.

Dr. Smith, you asked the question of if there was marked decrease of transcranial Doppler before occlusion. And, strangely enough, I do not recall that patient with a severe ischemia level before occlusion. I had not thought of it. But should that occur, based on this, I think that I would probably shunt them. I do not know the relative costs of the transcranial Doppler and the electroencephalogram (EEG). In the study, we have been working with the Department of Neurology. As far as a routine hospital charge, I do not know what it is. I agree with you that using both procedures, EEG and transcranial Doppler, is, as far as widespread general usage, probably overkill as regards the cost.

Dr. Edwards, the procedure that we use for patients that have difficulty after carotid is the same as yours, namely, that we let them wake up on the table. Those that do not are immediately re-explored, and those that have any difficulty in the recovery room are re-explored. I do a follow-up arteriogram after the endarterectomy or digital subtraction arteriogram, which gives me some assurance that maybe technically it has been all right. I appreciate the discussants. Thank you.

Neurotensin Augments Intestinal Regeneration After Small Bowel Resection in Rats

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Massive small bowel resection (SBR) is characterized by increased proliferation of residual gut mucosa and pancreas. Neurotensin (NT), a gut tridecapeptide, stimulates growth of normal gut mucosa and pancreas. This study examined whether NT affected growth of the small intestine and the pancreas after either distal or proximal SBR. Male Fischer 344 rats were divided into four groups. Group 1 underwent ileal transection with reanastomosis (SHAM) and group 2 underwent 70% distal SBR. Group 3 underwent SHAM operation (jejunal transection), and group 4 underwent 70% proximal SBR. After operation, each group was further subdivided to receive either saline (control) or NT (300 μg/kg) subcutaneously in gelatin every 8 hours for 7 days. At death, the pancreas and proximal jejunum (from groups 1 and 2) or distal ileum (from groups 3 and 4) were removed, weighed, and analyzed for DNA, RNA, and protein content. Both proximal and distal SBR significantly increased mucosal growth in the remnant intestine; a more pronounced effect was noted with proximal SBR. Administration of NT significantly augmented the adaptive changes in both groups of rats by mechanisms involving increases in both cell size (hypertrophy) and cell number (hyperplasia). Pancreatic growth was stimulated by distal (but not proximal) SBR; NT did not augment this response. The authors conclude that NT augments intestinal growth after SBR by mechanisms involving an increase in overall mucosal cellularity. Administration of NT may be therapeutically useful to enhance mucosal regeneration during the early period of adaptive hyperplasia after SBR.

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RESECTION OF THE small bowel in rats induces compensatory hyperplasia of the remaining gut mucosa.[1-3] These changes, beginning as early as 48 hours after resection, include an increase in the production rate of crypt cells, villus enlargement, and enhanced absorption.[1-5] The specific signals controlling this adaptive response are thought to include such factors as luminal nutrients,[6] pancreaticobiliary secretions,[7] and humoral factors.[8-10] In addition to the adaptive changes noted in the remnant of intestinal mucosa, small bowel resection is also associated with a stimulation of pancreatic growth that appears to be due, in part, to elevated levels of cholecystokinin, a potent pancreatic trophic factor.[11,12]

Neurotensin (NT), a tridecapeptide, is localized mainly in the central nervous system and in endocrine cells (N cells) of the gut mucosa in the jejunum and ileum.[13] The functions of NT in the gut include stimulation of pancreatic and biliary secretions[14] and inhibition of small bowel and gastric motility.[15] In addition, NT is trophic for several tissues in the gastrointestinal tract, including pancreas,[16,17] colon,[18] and small bowel.[19-21] Administration of NT stimulates mucosal growth in rats fed normal laboratory chow,[19] and prevents mucosal hypoplasia in rats fed an elemental diet.[20,21] Also, NT may be involved in the early stages of intestinal regeneration after small bowel resection.[22-24] Collectively, these data suggest an important role for NT as a potent enterotrophic factor and as a contributing factor to the growth of other gastrointestinal tissues.

The purpose of this study was to determine whether NT could affect intestinal regeneration and pancreatic growth after resection of either the proximal or distal small bowel.

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Materials and Methods

Experimental Design

Ninety-six male Fischer 344 rats (3 to 4 months of age, 170 to 280 g, National Institute of Aging, Bethesda, MD) were housed at a constant temperature (22 C) and humidity with 12-hour light and dark cycles. During this period, all rats were fed standard laboratory chow (Formulab Chow, Purina Mills, Inc., St. Louis, MO) *ad libitum*.

After at least a 7-day period of acclimation, rats were fasted overnight, weighed, and divided into four groups. Rats were anesthetized with an intraperitoneal injection of pentobarbital (40 mg/kg body weight). The abdomen was opened by a midline incision, and the small intestine was carefully measured along the antimesenteric border. Sham-operated transection controls underwent either ileal transection 5 cm proximal to the cecum (group 1) or jejunal transection 5 cm distal to the ligament of Treitz (group 3), without any intestine removed, followed by reanastomosis. Rats in group 2 underwent a 70% distal small bowel resection (DSBR) (approximately 65 cm of small bowel), beginning 5 cm proximal to the cecum. Rats in group 4 received a 70% proximal small bowel resection (PSBR), beginning 5 cm distal to the ligament of Treitz. In all groups, intestinal continuity was restored by end-to-end enteroenterostomy with 7–0 interrupted silk sutures. The abdomen was closed in one layer with 3–0 silk sutures. After operation, all rats were given 10 mL saline subcutaneously and allowed free access to water beginning 24 hours after operation. Sham-treated rats were pair-fed to the resected groups starting on postoperative day 3.

Beginning the morning of postoperative day 2, rats in each of the four study groups were further subdivided to receive subcutaneous injections of either saline (control) or NT (300 μg/kg, Bachem Inc., Torrance, CA) every 8 hours for 7 days.

Peptide Preparation

A stock solution of NT was prepared by first dissolving the amount of NT needed for the study in 1 mL of sterile water containing 0.1% (wt/vol) bovine serum albumin (Calbiochem-Behring, La Jolla, CA) and then diluted to the required concentration with saline containing 0.1% bovine serum albumin. Equal portions of this solution, sufficient for a single injection of all animals of a given group, were stored in glass vials at −20 C. Saline containing 0.1% bovine serum albumin (control) was likewise divided into equal aliquots and stored at −20 C. To prolong absorption, saline or NT was mixed 1:4 (vol/vol) with 15% (wt/vol) hydrolyzed gelatin (Sigma Chemical Co., St. Louis, MO) before administration.

Tissue Collection

The last injections were given at midnight on the eighth postoperative day. After an overnight fast, rats were weighed and then killed by decapitation beginning at 8:00 A.M. on postoperative day 9. The abdomen was opened and the proximal jejunum (20 cm) from groups 1 and 2, or distal ileum (20 cm) from groups 3 and 4, was removed. All segments were suspended vertically with a 15-g weight to ensure constant lengths. The mesentery was trimmed and luminal contents were removed by flushing with cold saline and gentle manual stripping. Each segment was then blotted dry, weighed, and the mucosa carefully scraped from the underlying seromuscular layer on a chilled platform, using a glass slide. In addition, the pancreas was removed from all rats and weighed. All specimens were immediately frozen at −70 C until assayed for DNA, RNA, and protein content.

DNA, RNA, and Protein Determination

Tissues were thawed and homogenized. The DNA content was measured by the Burton[25] modification of the diphenylamine procedure with calf thymus DNA used as the standard. Ribonucleic acid content was measured by means of the orcinol procedure with yeast RNA as the standard.[26] Protein content was determined by the method of Lowry and colleagues,[27] with bovine serum albumin as the standard.

Statistical Analysis

Mucosal and pancreatic weights and DNA, RNA, and protein contents were normalized to kilograms of body weight and values expressed as mean ± standard error of the mean. The data were analyzed by the two-way classification analysis of variance. The two classifications were defined as operation (SHAM and small bowel resection) and injection (saline and NT). The least significant procedure was used for mean separation. In all instances, a p value < 0.05 was considered significant.

Results

Body Weight

None of the groups of rats developed diarrhea; however, four rats died after DSBR and six rats died after PSBR because of anastomotic leakage. There was an approximately 5% to 6% weight decrease in both groups of rats that had small bowel resection compared with corresponding SHAM groups. There were no differences in body weights of NT and saline-treated rats within groups.

Effect of NT on Proximal Small Bowel Mucosa After DSBR

Distal small bowel resection alone significantly stimulated mucosal growth in the proximal jejunum (Fig. 1). Mucosal weight was increased by 34%, DNA content by 24%, RNA content by 32%, and protein content by 37% compared with the comparable sham group given saline injections. Neurotensin injections, administered to rats after DSBR, significantly augmented the response of the gut mucosa to resection alone. Indices of gut mucosal growth were all increased (weight by 23%, DNA content by 12%, RNA content by 22%, and protein content by 24%) compared with the values obtained in rats treated with DSBR and saline. As expected, NT given to rats after sham operation significantly stimulated gut mucosal growth.

Effect of NT on Distal Small Bowel Mucosa After PSBR

Proximal small bowel resection provided a stronger stimulus to intestinal adaptation than did distal resection (Fig. 2). Values of weight, DNA, RNA, and protein content were increased 50% to 70% over corresponding values in sham rats given saline injections. Even though PSBR produced a more pronounced increase in mucosal growth than DSBR, NT administration significantly augmented this response. Mucosal weight was increased by 23%, DNA content by 20%, RNA content by 21%, and protein content by 26% compared with rats treated with PSBR and saline injections.

Figure 3 summarizes and compares the effects of bowel resection either alone or combined with NT on mucosal growth in the residual gut.

Effect of NT on Pancreatic Growth After DSBR

Resection of the distal 70% of the small bowel stimulated increases of pancreatic weight (17%), DNA (15%) and RNA (28%) compared with sham operation (Fig. 4). In contrast to the small bowel mucosa, administration of NT did not augment pancreatic growth. Administration of NT to sham-treated rats resulted in significant increases of pancreatic weight (18%), RNA (14%), and protein (19%) compared with sham rats treated with saline.

Effect of NT on Pancreatic Growth After PSBR

Resection of the proximal small bowel resulted in a small (8%), but significant, increase in pancreatic DNA content (Fig. 5). Values of weight, RNA, and protein were not affected. Neurotensin treatment to sham and PSBR rats resulted in significant increases of growth measurements.

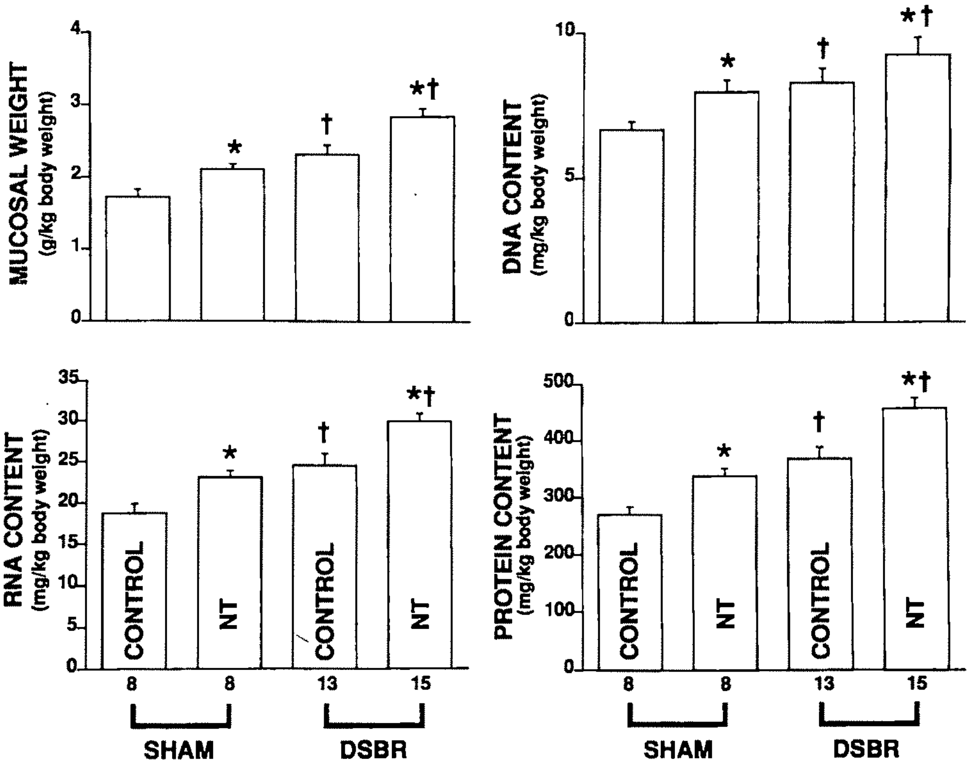

FIG. 1. Mucosal weight, DNA, RNA, and protein content of proximal jejunum (20 cm) from rats after either sham operation or 70% distal small bowel resection (DSBR). Rats were further subdivided to receive injections of saline (control) or NT (300 μg/kg). *p < 0.05 (NT vs. control); †p < 0.05 (DSBR vs. sham control).

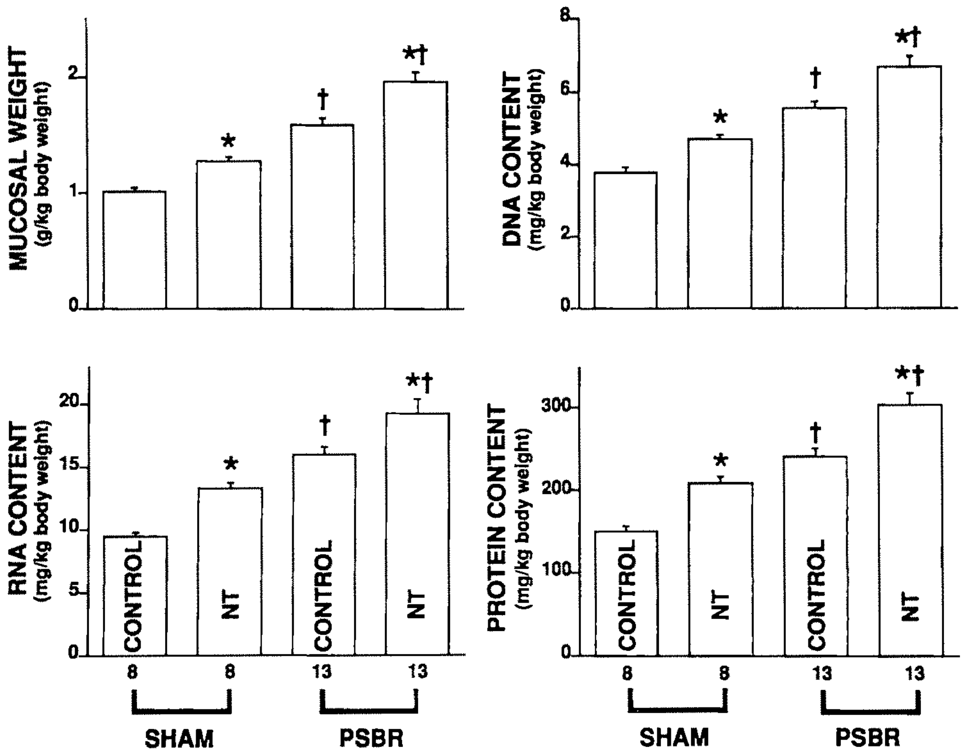

FIG. 2. Mucosal weight, DNA, RNA, and protein content of distal ileum (20 cm) from rats after either sham operation or 70% proximal small bowel resection (PSBR). Rats were further subdivided to receive injections of saline (control) or NT (300 μg/kg) *$p < 0.05$ (NT vs. control); †$p < 0.05$ (PSBR vs. sham control).

Discussion

Our findings demonstrate that NT (300 μg/kg) can augment gut adaptive hyperplasia that occurs after either proximal or distal small bowel resection. Neurotensin significantly increased mucosal weight, protein, and RNA content, indicators of cellular hypertrophy, and in addition, stimulated actual cellular proliferation, as demonstrated by the increases of DNA content.

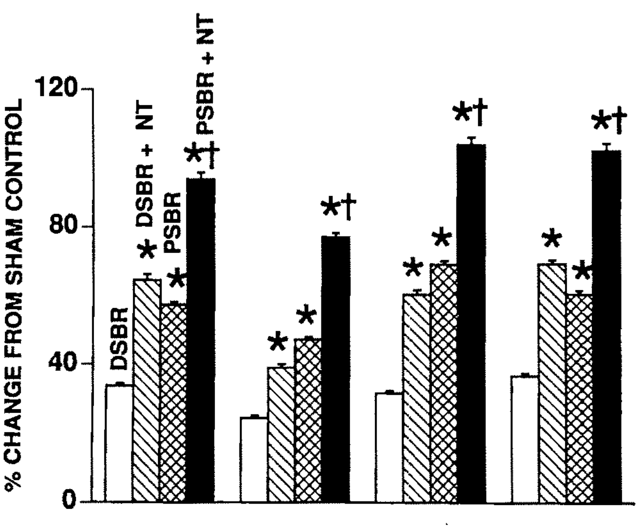

FIG. 3. Summary of changes of mucosal weight, DNA, RNA, and protein content after either distal small bowel resection (DSBR, open bar) or proximal small bowel resection (PSBR, double-hatched bar) alone or combined with NT injections. *$p < 0.05$ vs. DSBR; †$p < 0.05$ vs. PSBR.

Adaptive hyperplasia of intestinal mucosa occurs after extensive small bowel resection.[1-5,28] The residual intestine undergoes adaptive changes, both structural and functional, which include small bowel dilation, epithelial cell hyperplasia, and enhanced absorption.[1-10,28] Increases in DNA and RNA content are noted as early as 2 days after resection.[4,5] In our current study, we found significant increases in weight, DNA, RNA, and protein content in the remaining intestinal mucosa 9 days after either proximal or distal intestinal resection. Consistent with other reports,[1,29] we found a differential trophic response of the residual jejunum and ileum. Mucosal growth was increased 50% to 70% in the ileum after proximal small bowel resection compared with 25% to 35% increases of mucosal growth in the jejunum after distal small bowel resection. The reason for this differential effect is not known, but may be due, in part, to a greater supply of nutrients delivered to the remaining ileum. Because NT is found in highest concentration in the distal ileum, another possibility to explain why the proximal mucosa is less responsive may be that most of NT-containing gut is removed by a distal resection.

Signals controlling the compensatory hyperplasia of gut

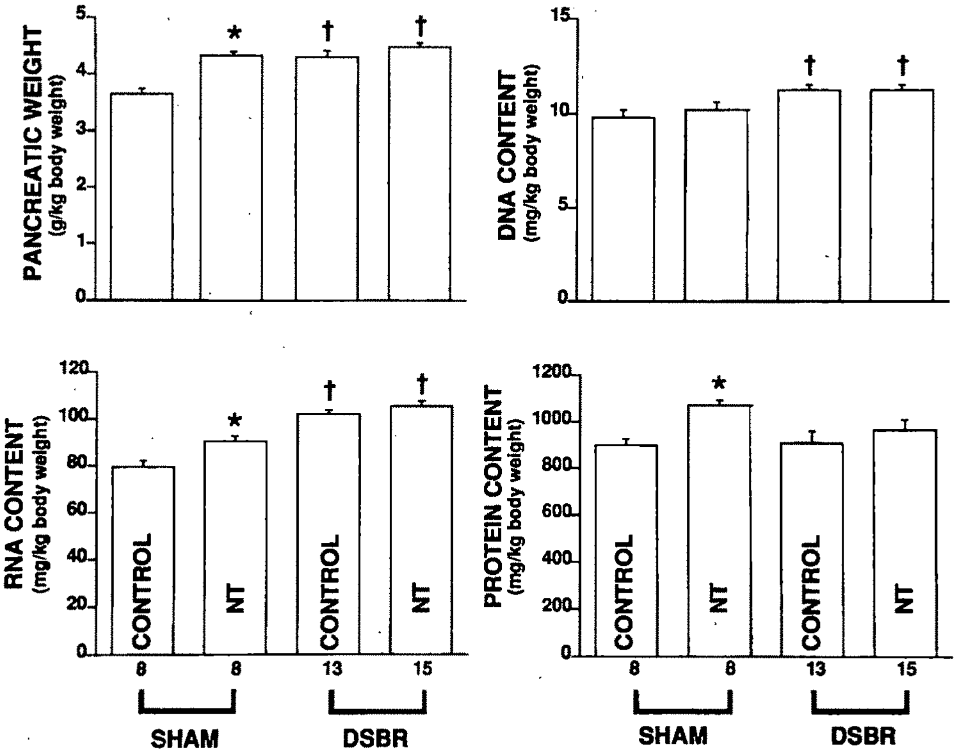

FIG. 4. Pancreatic weight, DNA, RNA, and protein content from the same animals shown in Fig. 1. *p < 0.05 (NT vs. control); †p < 0.05 (DSBR vs. sham control).

mucosa are complex; factors that appear to be important for a maximal trophic response include intraluminal factors (for example, luminal nutrients and pancreaticobiliary secretions).[6,7] Humoral factors also appear to play an important role in small bowel adaptation, a role that has been demonstrated dramatically by Williamson and colleagues[8] in parabiotic rats. Several gastrointestinal hormones, including gastrin and enteroglucagon, have been considered as potential candidates in the response to resection, but the evidence is largely inferential.[10,30,31]

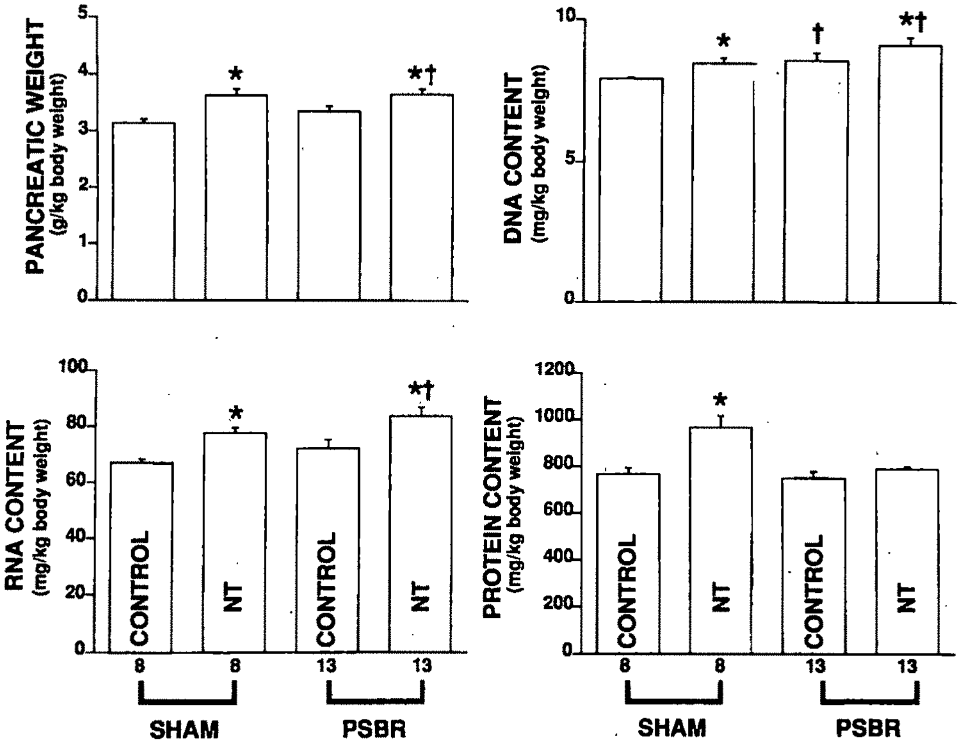

FIG. 5. Pancreatic weight, DNA, RNA, and protein content from the same animals shown in Fig. 5. *p < 0.05 (NT vs. control); †p < 0.05 (PSBR vs. sham control).

Another potential candidate for the humoral stimulation of gut mucosal growth after resection is NT. Neurotensin stimulates growth of both normal and atrophic gut mucosa,[19–21] and NT levels have been shown to be closely linked to the proliferative status of the small bowel mucosa.[22,24,32,33] We and others have shown that exclusion of nutritional stimuli to the small bowel mucosa during administration of an elemental diet or after heterotopic small bowel transplantation causes mucosal atrophy and a marked decrease in NT protein content[32] and N cell number[33] in the ileum. In contrast, small bowel resection induces hyperplasia in the remaining gut mucosa. We did not measure tissue levels of NT in the present study, but we have previously found that NT mRNA levels are increased in the rat ileum as early as 3 hours after proximal small bowel resection,[24] and Olsen and colleagues[22] have shown that the concentration of NT increases 3- to 15-fold in the residual gut after small bowel resection.

We have demonstrated here, for the first time, that NT augments the adaptive hyperplasia that occurs in gut mucosa after resection. Administration of NT for 7 days significantly increased weight, DNA, RNA, and protein contents after either proximal or distal enterectomy. Maximal gut hyperplasia occurs in the residual gut within 7 to 8 days after resection[4,5]; therefore, NT can further stimulate the proliferative response achieved by small bowel resection alone. Other studies have examined the effect of small bowel resection combined with administration of epidermal growth factor and prostaglandin E_2, agents reported to stimulate small bowel mucosa; however, these agents did not enhance mucosal regeneration of the distal gut when combined with intestinal resection.[34,35]

The mechanisms responsible for the augmentation of gut growth with NT in our study are not known. We have previously demonstrated that NT can stimulate mucosal growth by a direct systemic effect and also indirectly by the stimulation of pancreaticobiliary secretions[20]; therefore, a combination of factors may be involved.

In addition to stimulation of gut mucosal growth, resection of the distal (but not proximal) small bowel produces pancreatic hyperplasia.[11,12] Administration of the cholecystokinin antagonist CR-1409 suppresses this increase in pancreatic growth measurements, suggesting that increased cholecystokinin levels, which occur due to loss of the normal feedback control exerted by bile salts, are responsible for this phenomenon.[12] We found increases of pancreatic weight, DNA, and RNA content after distal small bowel resection in our current study. Neurotensin, trophic for normal pancreas, stimulated pancreatic growth in all sham-treated rats and rats treated with proximal small bowel resection. Neurotensin did not augment pancreatic growth after distal small bowel resection, however. These findings suggest that pancreatic growth stimulation was maximal and that administration of a perhaps weaker pancreatic trophic factor (NT) was unable to further augment this response.

Intestinal adaptation, after small bowel resection, also occurs in humans[28]; mucosal surface area may increase fourfold in the remaining gut. This adaptive response is oftentimes sufficient to compensate for limited resections of the intestine, but massive small bowel resection (*i.e.*, greater than 70%) is associated with increased morbidity and mortality rates because of a marked loss of intestinal absorptive surface.[36] Efforts to increase intestinal surface area have included innovative surgical techniques, such as longitudinal small bowel division and lengthening, construction of valves, and reversed segments of small bowel or colon, and small bowel transplantation.[37,38] These attempts have been, for the most part, unsuccessful. Identification of an agent that could augment the adaptive response of the residual gut after resection would be clinically important and may have potential therapeutic applications.

In conclusion, we have shown that both extensive small bowel resection and NT can independently increase gut mucosal growth. Administration of NT can further augment this adaptive hyperplasia of the remaining gut mucosa. Neurotensin appears to be an important enterotrophic factor and may be a useful agent during the early period of gut adaptation after resection of the small bowel to enhance mucosal regeneration.

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DISCUSSION

DR. LESTER WILLIAMS (Nashville, Tennessee): Dr. Ochsner, Dr. Jones, Members and Guests, I have had the pleasure of reading the manuscript, which contains not only the material you heard but considerable additional information. And as one would expect as we hear presentations from Dr. Thompson's laboratory, we have seen a magnificent presentation of the data, and I could find almost nothing to quibble with, with respect to the data. So I have three questions, one of which is not fair because he did not have a chance to present the pancreas data.

The first question is whether the assumption is that neurotensin's mechanism is predominantly by a direct, systemic effect. If that is true, is it possible that the difference between the distal resection and proximal resection data could have been negated by increasing the dose of the exogenous neurotensin? Or do you have reason to believe that the mechanism is somehow or other different? If in fact it is simply a matter of the amount of neurotensin that is still in the animal because the distal bowel is there, then you would expect to be able to overcome these differences by increasing the exogenous dose.

The second question relates to the consequence of these changes in cellular phenomena. We do not have evidence that these cellular changes made a difference. Is there any functional significance to the cellular change? In fact, the all of resected animals lost weight, 5% to 6%. There was not a difference between the amount of weight lost in the animals that received neurotensin and those that received saline, and yet, the effect in terms of cellular phenomena were better with the neurotensin. Why did we not see functional significance in terms of the effect with treatment of these animals?

It is also true that in the manuscript you will see some information on the pancreas. And the fascinating phenomenon is that the pancreas goes differently than what would be predicted. The paper, I think, perhaps contains other evidence of a mechanism that we would have to explain. I certainly enjoyed the opportunity to see the manuscript and discuss the paper. Thank you.

DR. HIRAM POLK (Louisville, Kentucky): Mr. President, Dr. Jones, It is an interesting commentary to think back over 20 years ago and realize that the observations of Drs. Ellison and Zollinger would turn into this kind of sophisticated analysis of what now is the most important endocrine organ in the body, that is, the alimentary tract. It is an interesting turnaround from a thoughtful, clinical observation to something that is now fairly fundamental basic science. This paper is pretty typical of the work that Dr. Thompson, Dr. Townsend, and Dr. Evers have done in recent years. I do think that the questions and implications, however, are great.

There are some issues about the timing and duration of treatment. In other words, how late could you begin this treatment with potential value? And then how long should it be continued? Does it have a continued proliferative effect or does it plateau? I think the point that Dr. Williams made about functional significance is important, and it would be nice to see this sort of thing applied to a critical small bowel resection, the kind that would be incompatible with growth and normal life and to see if you could moderate that in a functional way, just as Drs. Dudrick and Rhoads did with parenteral hyperalimentation so long ago. Could it make the difference? Because it is clear that this is a very uncommon problem in the adult, but it is not an uncommon problem in the child, and I think that there are a number of individuals who face radical therapy. I mean either home hyperalimentation or transplantation, both of which are presently radical undertakings and might be modified in this situation if applicable to the child with necrotizing enterocolitis or massive mid-gut volvulus. I think it will be interesting to see whether this treatment administered over a longer period is beneficial in that setting. Potentially it is very valuable and, of course, it is very instructive about the basic fundamentals of alimentary tract endocrinology. Thank you very much.

DR. R. SCOTT JONES (Charlottesville, Virginia): Thank you, Dr. Ochsner. I had a couple of questions that I wanted to ask about this excellent presentation. Would the authors put this material in perspective from the standpoint of physiologic control mechanisms. In other words, the experiment demonstrates that exogenously administered neurotensin stimulated hyperplasia and hypertrophy in the remaining small bowel. I would like to know whether you have any evidence about whether this is a physiologic phenomenon. In other words, is neurotensin responsible for the hyperplasia that occurs after small bowel resection?

And I would be interested to know whether there are any changes in the levels of this substance in the blood to suggest that it acts like a hormone?

The second question is unrelated to your primary experiment, but I would appreciate hearing your thoughts on it. There are a number of other changes that occur in gastrointestinal function after small bowel resection, and one of those is increased acid secretion. Neurotensin, as you indicated, does not stimulate acid secretion. Indeed, I guess it may inhibit it, and it delays gastric emptying. Please make a comment that might correlate the changes that occur in neurotensin with the changes that occur in acid secretion. I really enjoyed hearing your presentation, and want to compliment the authors on an excellent piece of work. Thank you.

DR. B. MARK EVERS (Closing discussion): Thank you, Dr. Ochsner, Dr. Jones. Dr. Williams, both of your questions really relate to whether we have looked at different dosages and different time schedules. You first asked about the mechanisms and whether we have tried increasing the dose to see if we can overcome the effects of the proximal *versus* the distal resection. We have found actually that neurotensin has a fairly complex mechanism of action, including both direct and indirect effects. We have not tried increasing the dosage; however, that is planned for future studies. In this initial study, we used the standard dosage of 300 μg/kg, which we and other laboratories have shown has a maximal effect.

Dr. Polk, you asked about a time course study. We have looked at a time course study with different dosages of neurotensin in rats without small bowel resection. We found that we get a maximal effect of neurotensin on gut growth by 5 to 7 days, at which time a plateau is reached. Dr. Jones and Dr. Polk both asked about functional significance of the neurotensin. The only thing that we have studied from a functional standpoint is that we have found that neurotensin increases activity of certain disaccharidases. This has also been shown by Travis Solomon in Kansas City.

Dr. Jones, you asked about a physiologic phenomenon, whether neurotensin could be responsible for changes after small bowel resection. We think that neurotensin may contribute to the changes seen after small bowel resection. The evidence for that includes a paper by Olson and colleagues that shows that neurotensin content is increased after small bowel resection. There have been both experimental and clinical studies that show that neurotensin blood levels increase after small bowel resection, and we have shown and presented at the Surgical Forum that the actual messenger RNA for neurotensin increases by 3 hours and is up again at 24 hours after resection, so that is certainly something we are investigating in our laboratory now. Thank you very much.

The Effect of Gastrin on Growth of Human Stomach Cancer Cells

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Gastrin is known as a trophic factor for some stomach and colorectal cancer cells; however, the roles of gastrin receptors and the intracellular signal transduction pathways by which gastrin regulates cell growth are still unknown. The authors examined the effect of synthetic human gastrin-17 on growth of human stomach cancer cells (the parent line, AGS-P, and two different clones, AGS-10 and AGS-12), which were established (and have been maintained) in our laboratory. Gastrin stimulated growth of AGS-P and AGS-10 cells, which have gastrin receptors, in a dose-dependent fashion. A highly selective gastrin receptor antagonist, JMV 320, inhibited the growth-stimulatory effect of gastrin on AGS-P cells in a dose-dependent fashion. Concentrations of gastrin (10^{-8} to 10^{-6} M), which stimulated growth of AGS-P cells, did not affect either cyclic adenosine monophosphate production or phosphatidylinositol hydrolysis. Gastrin (10^{-11} to 10^{-5} M) mobilized calcium from the intracellular organelles to increase intracellular calcium level in AGS-P cells. The AGS-12 clone has no gastrin receptors, and gastrin did not affect growth or mobilization of intracellular calcium in these cells. Our findings indicate that gastrin stimulates growth of AGS cells through a mechanism that involves binding to specific gastrin receptors that are linked to the system for mobilization of intracellular calcium.

GASTRIN IS SYNTHESIZED and secreted from G cells in the antrum of the stomach and stimulates gastric acid secretion. There is no question that gastrin is also a trophic hormone. Johnson[1] clearly demonstrated the trophic effects of gastrin on mucosa of the rat gastrointestinal tract. Patients with the Zollinger-Ellison syndrome, which is characterized by hypergastrinemia, are known to show massive fundic mucosal hyperplasia.[2] The trophic effect of gastrin on a number of established stomach cancer cells has been well documented *in vivo* and *in vitro.*[3-6] The intracellular mechanisms of signal transduction by which gastrin affects growth of cancer cells are, however, still unclear. To determine the precise mechanism by which gastrin affects the growth of stomach cancer cells will undoubtedly be valuable for developing a new therapeutic strategy for patients with stomach cancer. Therefore, the purpose of the current study was to examine in-depth the effect of gastrin on the growth of human stomach cancer cells in terms of receptor–ligand interaction and postreceptor signal-transduction pathways.

A human stomach cancer cell line (termed AGS), which was established and has been maintained in our laboratory,[6] was employed as a target cell to examine the effect of gastrin in the current study. We have maintained two different cloned cell lines (AGS-10 and AGS-12) in addition to the polyclonal AGS parent (AGS-P) cell line. We have reported previously that both AGS-P and AGS-10 cells have gastrin receptors (AGS-P: 25.1 ± 5.7 fmol/100 μg DNA and AGS-10: 28.0 ± 0.7 fmol/100 μg DNA), and AGS-12 cells have none.[7]

Materials and Methods

AGS-P, AGS-10, and AGS-12 cells have been maintained in culture medium (F-10), containing fetal calf serum (FCS) in a humidified atmosphere of 95% air and 5% CO_2 at 37°C. Stock cultures have media changed every 3 days (the doubling times are approximately 20 hours for AGS-P and AGS-10 and 35 hours for AGS-12). Human gastrin-17 was purchased from Bachem, Torrance, California. Gastrin receptor antagonists were synthesized as previously reported[8-11]; JMV 56 is a phenethyl ester

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derivative analog of the C-terminal tetrapeptide of gastrin.[8] JMV 76 is a pseudo-peptide analog of tetragastrin.[9] JMV 97 is a partially modified retro-inverso pseudopeptide derivative of tetragastrin.[10] JMV 320 is a cyclic cholecystokinin analog that is highly selective for a central cholecystokinin receptor or a gastrin receptor.[11] The amino acid structures of all gastrin receptor antagonists employed in the current study are shown in Table 1. All experiments were performed using six dishes or wells (one cover slip for the calcium study) in each experiment, and each study was repeated on at least three separate occasions. Representative data from each experiment are shown in this paper.

Effect of Human Gastrin-17 and Gastrin Receptor Antagonists on Growth of AGS-P, AGS-10, and AGS-12 Cells

AGS-P, AGS-10, and AGS-12 cells (2×10^4) were plated in F-10 containing 5% FCS. After 48 hours, cells had medium replaced by F-10 containing 1% FCS. After 24 hours, gastrin-17 (10^{-8} to 10^{-6} M) and a gastrin receptor antagonist, either JMV 56 (10^{-5} M), JMV 76 (10^{-5} M), JMV 97 (10^{-5} M) or JMV 320 (10^{-7} to 10^{-5} M), were added alone or in combination. Each peptide or vehicle (0.03 N NH_4OH for gastrin and distilled water for gastrin receptor antagonists) was added only once at the first day of the experiment or added every other day. Every other day, cells were detached from culture dishes with trypsin (1:250, Gibco) and diluted 10-fold with Isoton (Curtin Matheson Scientific, Houston, Texas). The cell number was counted by a Coulter counter, which was electronically set to count cells under 100 μm in size. The number of cells determined by the Coulter counter was similar (less than 5% difference) to the number of viable cells determined by a dye (trypan blue)-exclusion method using a hemocytometer. Also, the coefficient variances of low and high counts determined by this electric counter were less than 2%.

Effect of Human Gastrin-17 and JMV 320 on Phosphatidylinositol Hydrolysis in AGS-P Cells

Phosphatidylinositol (PI) hydrolysis was measured following a protocol adapted from Hawkins and colleagues.[12] In brief, AGS-P cells (3×10^5), which were plated and cultured in 24-well tissue culture plates for 2 days, were incubated with F-10 containing 5% FCS supplemented with myo-3H-inositol (10 μCi/mL) for 16 hours. Cells were then incubated for 10 minutes with oxygenated Krebs-Ringer bicarbonate buffer (pH 7.4) containing HEPES (10 mM), bovine serum albumin (0.1%), glucose (2.5 mM) and LiCl (10 mM). After another 1-minute incubation in the presence of human gastrin-17 (10^{-7} to 10^{-5} M), cells were extracted with 10% perchloric acid and immediately neutralized with 6 N KOH. Fractions of inositol monophosphate (IP_1), inositol bisphosphate (IP_2), inositol trisphosphate (IP_3), and inositol tetrakisphosphate (IP_4) were extracted by anion exchange chromatography (Dowex AG-1 × 8; formate form; 200 to 400 mesh) using a mixture of formic acid and ammonium formate as an eluent. After a fraction of inositol was eluted by an excess of water, IP_1, IP_2, IP_3, and IP_4 were eluted by 0.1 M formic acid ± 0.2 M ammonium formate, 0.1 M formic acid ± 0.4 M ammonium formate, 0.1 M formic acid ± 1.0 M ammonium formate, and 0.1 M formic acid ± 1.6 M ammonium formate, respectively, in a stepwise fashion. Radioactivity of each fraction was measured by a liquid scintillation counter.

TABLE 1. *Amino Acid Structures of Gastrin-Receptor Antagonists*

Antagonist	Structure
JMV 56	Boc-Trp-Leu-Asp-2-phenethyl ester
JMV 76	Boc-Trp-LeuΨ(CH_2NH)-Asp-Phe-NH_2
JMV 97	Boc-Trp-Leu-gAsp-CO-$CH_2CH_2C_6H_5$
JMV 320	Acetyl-Tyr-Lys-Gly-Trp-Lys-Asp-Phe-NH_2

Effect of Human Gastrin-17 and JMV 320 on the Production of Cyclic Adenosine Monophosphate in AGS-P Cells

AGS-P cells (5×10^5) were plated and cultured in 35- × 10-mm tissue culture dishes for 2 days, incubated in oxygenated Krebs-Ringer bicarbonate buffer (pH 7.4) containing HEPES (10 mM), bovine serum albumin (0.1%), glucose (2.5 mM), and IBMX (0.1 mM). After 30-minute incubation in the presence of human gastrin-17 (10^{-8} to 10^{-5} M) alone or with JMV 320 (10^{-5} M), cells were extracted with 5% trichloroacetic acid and neutralized with an excess of $CaCo_3$ just before radioimmunoassay.[13] After acetylation of samples with acetic anhydride and triethylamine, intracellular cyclic adenosine monophosphate (cAMP) levels were measured by cAMP radioimmunoassay kit (Amersham Corporation, Arlington Heights, IL).

Effect of Human Gastrin-17 and JMV 320 on the Mobilization of Intracellular Calcium in AGS-P and AGS-12 Cells

AGS cells were grown on 25-mm diameter glass coverslips at 37 C in F-10 medium supplemented with 5% FCS. The coverslips were coated with 25% Matrigel (Collaborative Research Inc., Bedford, MA) solution to enhance attachment of cells. The cells were incubated for 60 minutes at 25 C with 2 mL Krebs Ringer Henseleit (KRH) buffer containing 10 μM of fura-2/acetoxylmethyl ester. Krebs Ringer Henseleit contains, in millimoles per liter: NaCl, 125; KCl, 5; $MgSO_4$ and KH_2PO_4, 1.2; $CaCl_2$, 2; glucose, 6; Hepes 25, pH 7.4. Loaded cells were washed twice with fresh KRH and reincubated in KRH with 0.1% bovine serum albumin at 5 C for 30 minutes before fluorescence microscopy. The cells were placed in an open perfusion microincubator (PDMI-2) (Medical System Corp., Greenvale, NY) and stimulated by human gastrin-17 (10^{-12} to 10^{-5} M) diluted in either 0.5% FCS or normal saline at 37°C. Furthermore, to examine the effect of human gastrin-17 on mobilization of intracellular calcium, a calcium-free KRH solution with ethylene glycol tetra-acetic acid (5 mM) was employed as an incubation buffer instead of KRH. Fura-2 fluorescence intensity was measured using a dual-wavelength excitation spectrofluorometer (Spex Industries, Inc., Edison, NJ). The excitation light was obtained from a xenon high-pressure lamp at wavelengths of 340 nm and 380 nm (band width: 10 nm). Intracellular calcium was calibrated by lysing cells with 0.03% Triton X-100 and by using 5 nM ethylene glycol tetra-acetic acid. Concentration of intracellular calcium was calculated by the method of Grynkiewicz et al.,[14] using a Kd for calcium as 224 nM.

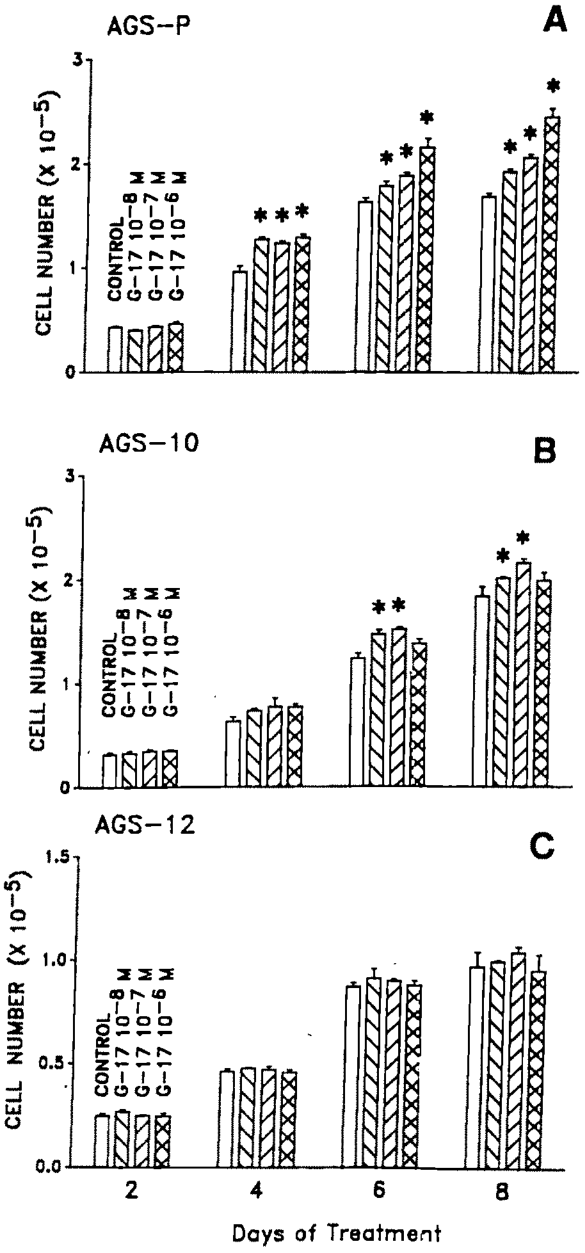

FIG. 1. Effect of human gastrin-17 on growth of (A) AGS-P, (B) AGS-10, and (C) AGS-12. In this figure and the following figures, error bars indicate standard error of the mean. *$p < 0.05$ *vs* control.

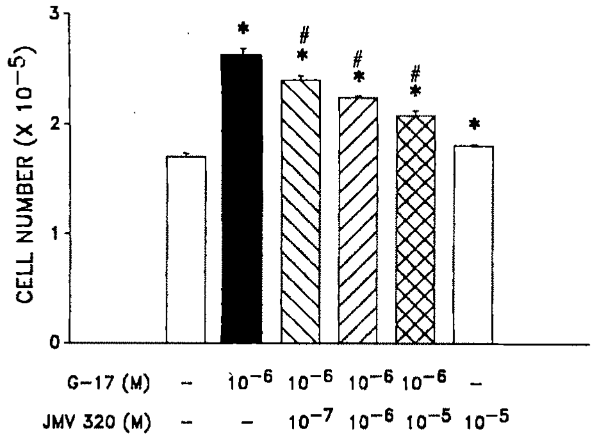

FIG. 2. Effect of JMV 320 on growth-stimulatory effect of gastrin on AGS-P cells. *$p < 0.05$ *vs.* control; #$p < 0.05$ *vs.* gastrin alone.

Statistical Analysis

Data from each study were analyzed by unpaired t test, and significance was assumed for p value less than 0.05.

Results

Effect of Human Gastrin-17 and Gastrin Receptor Antagonists on Growth of AGS-P, AGS-10, and AGS-12 Cells

Human gastrin-17 stimulated growth of AGS-P cells, which have gastrin receptors, in a dose-dependent fashion. Stimulatory effects became apparent at the fourth day after addition of gastrin and continued to the eighth day, when growth of cells without gastrin became confluent (Fig. 1A). Addition of gastrin every other day showed results similar to those of single addition of gastrin (data not shown). Growth of AGS-10 cells, which also have

TABLE 2. *Effect of Gastrin on Phosphatidylinositol (PI) Hydrolysis in AGS-P Cells*

	IP_1	IP_2	IP_3	IP_4
Control	1595 ± 37	657 ± 127	589 ± 58	350 ± 64 dpm
Gastrin 10^{-7} M	1450 ± 23	586 ± 100	564 ± 18	295 ± 29
Gastrin 10^{-6} M	1427 ± 70	599 ± 81	533 ± 28	278 ± 18
Gastrin 10^{-5} M	1507 ± 269	737 ± 35	598 ± 130	255 ± 45

IP_1, inositol monophosphate; IP_2, inositol bisphosphate; IP_3, inositol trisphosphate; IP_4, inositol tetrakisphosphate.

TABLE 3. *Effect of Gastrin on Cyclic AMP Production in AGS-P Cells*

	Cyclic AMP Level
Control	42.4 ± 1.2 pmole/10^6 cells
Gastrin 10^{-8} M	44.8 ± 3.4
Gastrin 10^{-7} M	44.3 ± 0.8
Gastrin 10^{-6} M	45.4 ± 2.8
Gastrin 10^{-5} M	43.2 ± 2.8

gastrin receptors, was similarly stimulated by gastrin, although a high concentration (10^{-6} M) of gastrin did not stimulate growth of AGS-10 cells (Fig. 1B). Conversely, growth of AGS-12 cells, which have no gastrin receptor, was not affected by gastrin at any doses tested (Fig. 1C).

The stimulatory effects of gastrin on AGS-P cells were inhibited by JMV 320 in a dose-dependent fashion (Fig. 2), but other gastrin-receptor antagonists (JMV 56, JMV 76, and JMV 97), did not affect the stimulatory effect of gastrin (data not shown). A high concentration (10^{-5} M) of JMV 320 itself also stimulated growth of AGS-P cells (Fig. 2), whereas other gastrin receptor antagonists did not affect growth of AGS-P cells (data not shown).

Effect of Human Gastrin-17 and JMV 320 on Phosphatidylinositol Hydrolysis in AGS-P Cells

With a short (1 minute) stimulation by human gastrin-17, PI hydrolysis in AGS-P cells did not occur; that is, the radioactive fractions of IP_1, IP_2, IP_3, and IP_4 in AGS-P cells stimulated by gastrin were similar to those in AGS-P cells without gastrin (Table 2). JMV 320 did not affect PI hydrolysis in AGS-P cells, either by itself or by gastrin (data not shown).

Effect of Human Gastrin-17 and JMV 320 on the Production of Cyclic Adenosine Monophosphate in AGS-P Cells

Gastrin (at all concentrations tested) failed to affect the production of intracellular cAMP (Table 3). Similarly, JMV 320 did not affect the production of cAMP (data not shown).

Effect of Human Gastrin-17 and JMV 320 on the Mobilization of Intracellular Calcium in AGS-P and AGS-12 Cells

Intracellular calcium level in a basal condition was 135 ± 22 nM in AGS-P cells, and the level in AGS-12 cells was similar (129 ± 18 nM). In the absence of 0.5% FCS, any concentration of gastrin did not affect intracellular calcium level in AGS-P cells at all; however, in the presence of 0.5% FCS, which by itself did not affect intracellular calcium level, gastrin stimulated the mobilization of intracellular calcium. Intracellular calcium level was increased by a range between 10^{-11} and 10^{-5} M of gastrin. Response to gastrin, however, was dependent on the concentration of gastrin. Both 10^{-10} M and 10^{-7} M of gastrin quickly increased intracellular calcium level, whereas 10^{-11}, 10^{-9}, 10^{-8}, 10^{-6}, and 10^{-5} M gastrin increased intracellular calcium level to a lesser degree (Fig. 3). Furthermore, the intracellular calcium levels increased with a time lag of response to these concentrations of gastrin, as shown in Figure 3. That is, intracellular calcium level of AGS-P cells responded to gastrin in a biphasic dose-dependent fashion (Fig. 4).

To further clarify whether the effect of gastrin is dependent on extracellular calcium, response to gastrin was

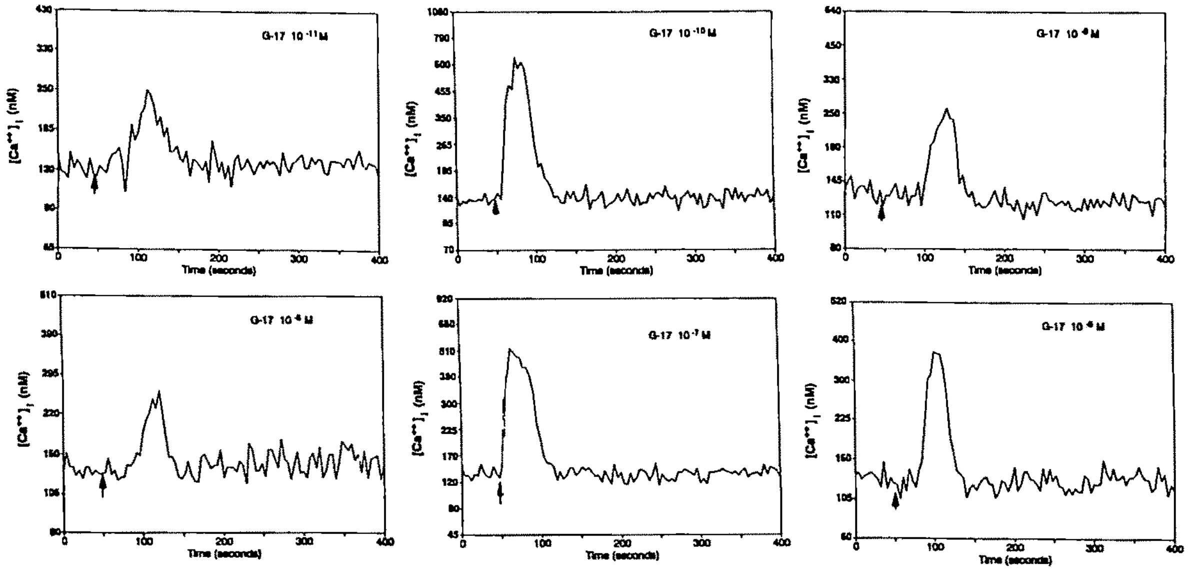

FIG. 3. Mobilization of intracellular calcium ($[Ca^{++}]_i$) in AGS-P cells in response to gastrin. Arrows indicate the time point when gastrin was added.

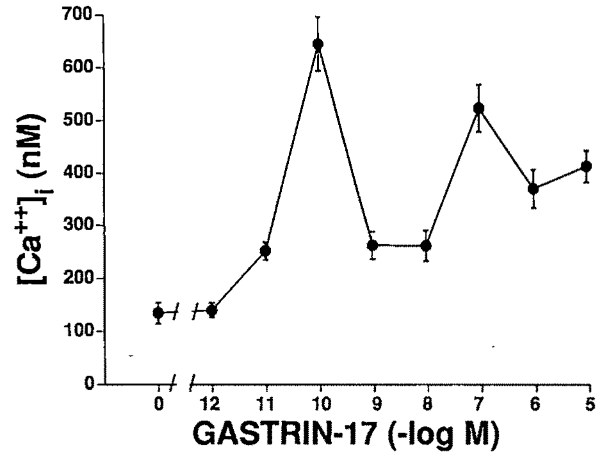

FIG. 4. Correlation between intracellular calcium level ($[Ca^{++}]_i$) and doses of gastrin in AGS-P cells.

examined in a calcium-free condition. As a result, even in a calcium-free condition, gastrin increased intracellular calcium level to a similar level to that in the presence of calcium in the extracellular fluid (Fig. 5).

Conversely, gastrin failed to increase the intracellular calcium level in AGS-12 cells that do not possess gastrin receptors (Fig. 6).

Discussion

To express their effects on cells, peptides must bind to specific cell membrane receptors that are linked to various intracellular signal transduction pathways, such as the cAMP pathway, the tyrosine kinase pathway, PI hydrolysis, or mobilization of intracellular calcium. The present findings indicate that growth-stimulatory effect of gastrin on human stomach cancer cells, AGS, are mediated through specific gastrin receptors that appear to be linked to the signal transduction pathway that involves mobilization of intracellular calcium.

In the current study, four different types of gastrin receptor antagonists were employed. Among those, only JMV 320 inhibited the growth-stimulatory effect of gastrin. JMV 320 is a cholecystokinin analog that is a highly selective antagonist for brain type of cholecystokinin receptor (Type II). Our findings, however, suggest that AGS-P cells have a third class of cholecystokinin receptor, which is found on parietal cells, gastric glands, and gastrointestinal smooth muscle cells.[15–21] This receptor has been reported to have approximately equal affinity for cholecystokinin and gastrin and is referred to as a gastrin receptor.[15–21] Thus, we have demonstrated that AGS-P cells have specific, functional gastrin receptors.

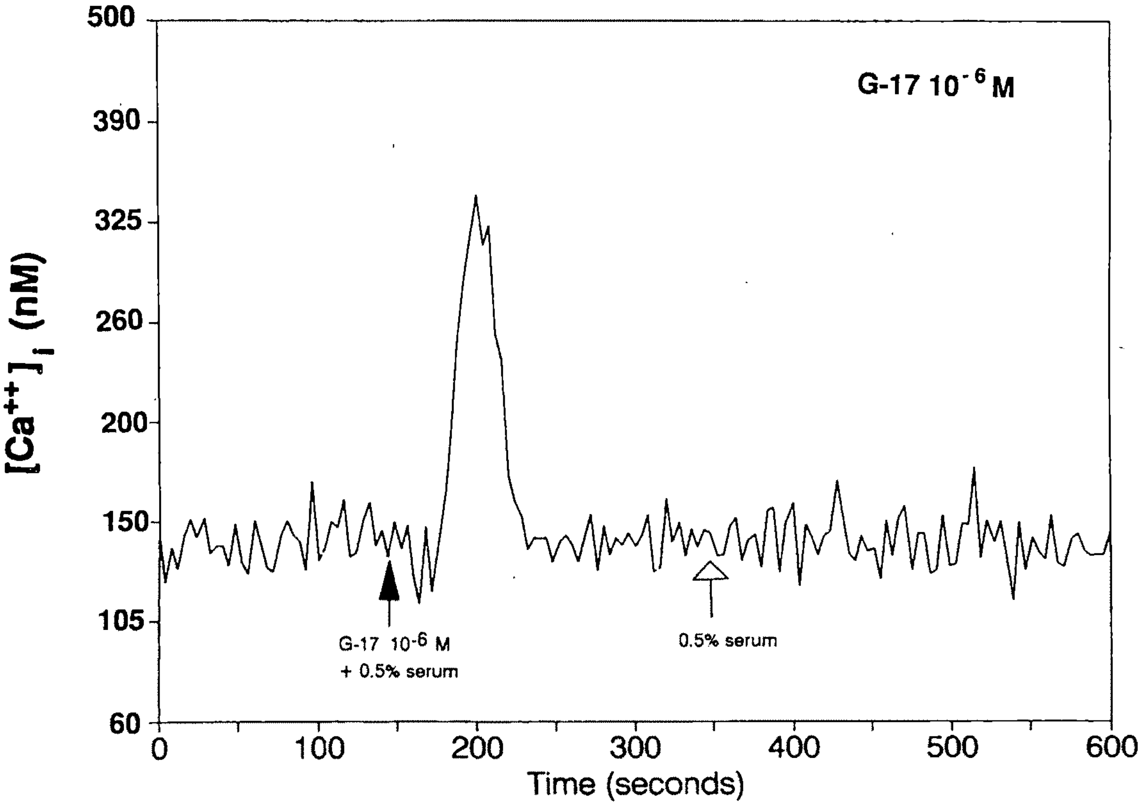

FIG. 5. Mobilization of intracellular calcium ($[Ca^{++}]_i$) in AGS-P cells in response to gastrin in calcium-free medium containing 5 mM ethylene glycol tetra-acetic acid.

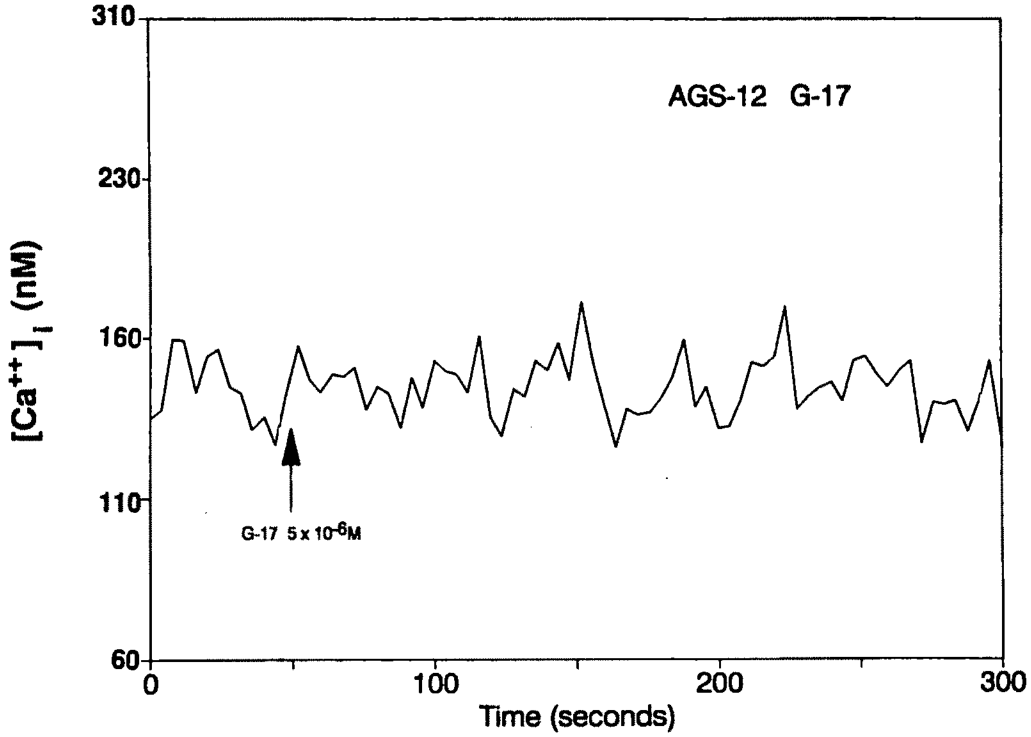

FIG. 6. Response of intracellular calcium ([Ca^{++}]$_i$) in AGS-12 cells to gastrin.

Kim and colleagues[22] have reported that vasoactive intestinal polypeptide inhibited growth of AGS-P cells through the intracellular second messenger, cAMP. Thus, when we found the growth-stimulatory effect of gastrin on AGS-P cells, we speculated that gastrin might inhibit the production of cAMP in AGS-P cells to express its growth-stimulatory effect. However, gastrin failed to affect the production of cAMP.

Phosphatidylinositol hydrolysis has been reported to play an important role in growth of certain cells.[23–25] In the current study, however, we found that gastrin did not affect PI hydrolysis in AGS-P cells.

Intracellular calcium is known to play an important role in growth of certain cells.[26] Gastrin clearly increased intracellular calcium levels in AGS-P cells in an unique, biphasic fashion. The reason for this unique response to gastrin is still unclear, but one explanation may be that AGS-P cells consist of at least two different populations of cells that have gastrin receptors with different sensitivities to gastrin. Although preliminary, we have found that the growth-stimulatory effect of gastrin is parallel to the mobilization of intracellular calcium (unpublished data). The product of PI hydrolysis, IP_3, is known to stimulate mobilization of intracellular calcium,[23] but our findings suggest that gastrin receptors on AGS-P cells are directly linked to the mobilizing system of intracellular calcium and are independent of PI hydrolysis. Furthermore, results obtained from the experiments using calcium-free medium indicate that gastrin elevated levels of intracellular calcium by mobilizing calcium mainly from the intracellular organelles, but not from the extracellular fluid through calcium influx.

There is no question that growth of normal and cancer cells are regulated by various factors through various intracellular signal transduction pathways. In the current study, we showed that growth of human stomach cancer cells was stimulated by human gastrin-17 through a specific gastrin receptor, and that the stimulatory effect of gastrin was mediated, at least in part, through mobilization of intracellular calcium from the intracellular organelles. Although the complete growth-stimulatory mechanism of gastrin remains to be clarified, this is the first report that gastrin stimulates growth of human stomach cancer cells through specific gastrin receptors that are linked to the system for mobilization of intracellular calcium.

Acknowledgments

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DISCUSSION

DR. KIRBY I. BLAND (Gainesville, Florida): President Ochsner, Dr. Jones, Fellows and Guests, I wish to begin the discussion of this important paper by thanking Dr. Townsend and his co-authors for allowing me to review this manuscript in advance. Their laboratory in Galveston has been responsible over a number of years for elucidating the stimulatory and inhibitor roles of a variety of polypeptides for several gastrointestinal cell lines. To my knowledge, however, this is the first report to document that gastrin stimulates the growth of human gastric cancer cells through specific gastrin receptors. We have seen in the presentation by Dr. Townsend that specific gastrin receptors are linked to the system that initiates mobilization of intercellular calcium. This paper, as have others from their laboratory, documents that growth of normal and neoplastic cells are regulated by various factors. These include interleukins and cytokines, and these pathways may augment or suppress signal transduction. I encourage the membership to review this manuscript because, again, a lot of data are included in that manuscript that Courtney did not have time to present.

Dr. Townsend also has emphasized that synthetic human gastrin 17 stimulates growth of the parent cell line, the AGSP, as well as the two clones, the variants 10 and 12, to varying degrees. Further, the highly selective receptor antagonists, JMV 320, statistically inhibit growth stimulatory effects on gastrin of this parenteral cell line. This effect is sustained in a dose-dependent fashion. Your data have convinced me, and they document that hormonal effects of gastrin by the PI hydrolysis as well as production of intracellular cyclic adenosine monophosphate are not responsible for the trophic or the stimulatory effects of growth of gastrin on human gastric cell lines. Also, the antagonist failed to effect PI hydrolysis and had no effect on cyclic adenosine monophosphate production. It is interesting, however, that of the four different types of gastrin receptor antagonists used, you found that only the 320 variant inhibited this growth stimulatory effect on gastrin 17. It is appropriate to note — and Courtney brought this out very clearly — that this receptor has equal affinity for gastrin as well as the cholecystokinin receptor, but we happen to refer to it in this model as the gastrin receptor. This laboratory has, therefore, documented that at a molecular level the parent neoplastic cell line has specific sites that function on gastrin receptors.

Courtney, I have a number of questions from these important observations you have made. Because intracellular calcium plays a prominent role linked to signal transduction pathways, this observation may account for the stimulatory role of gastric neoplastic cells in this model as well as, perhaps, other cell lines. Could you provide us with more data that explain the unique biphasic responses of gastrin to increased intracellular calcium? And linked to that question, secondly, is this biphasic response because of the heterogenous population of cell lines and their variation and binding sensitivity to gastrin?

And the next question, because we are interested, obviously, in transferring this technology to the bedside — and this is an *in vitro* model — have you completed any studies, at least any models generated thus far, as an *in vivo* preparation? And, finally, it would be interesting to know, would you anticipate other agents such as Losec (omeprasol, Merck, Sharp, and Dohme) or H_2 blockers to have a similar inhibitory role to block the trophic effects of gastrin *in vivo*? I enjoyed this paper very much, and I thank the Association for the privilege of the floor.

DR. JOSEF FISCHER (Cincinnati, Ohio): President Ochsner, Secretary Jones, Every medical student, even the ones that we currently educate — and that is saying quite a bit — knows that achlorhydria is associated with an increased incidence of carcinoma of the stomach. And I think this paper today probably goes a long way into elucidating that relationship. As Dr. Townsend pointed out in his really excellent presentation and in a very nice paper, this is not, however, a simple relationship. One of the things he showed in the slide and commented on in the manuscript was that a high dose of gastrin, 10^{-6} molar, does not stimulate the growth of cells. And, as he pointed out and elaborated on, high doses of JMV 320, 105 molar, stimulate the growth of gastric cancer cells. This suggests that the relationship is really not a simple one, and as Dr. Bland has already mentioned, the other three antagonists do not seem to have any effect at all on the inhibition of gastric cancer cell growth. Now it is true that JMV 320, judging from its structure, which is really quite different from the other antagonists, probably does have antagonist effect. So one could explain away the fact that it stimulated the gastric cell line growth a little bit at 10^{-5} molar. But the fact that gastrin at 10^{-6} molar did not stimulate the growth, I think, remains to be explained and suggests that this is a somewhat more complicated relationship than a one-to-one. In your manuscript, Dr. Townsend and Dr. Thompson, you also suggest that the relationship with calcium is also not a one-to-one relationship. Your 10^{-8} molar did not stimulate calcium very much and yet had a profound effect on the growth of cells. Some doses of gastrin stimulate calcium but not growth. And some doses of gastrin stimulate growth but not calcium. And so my first question to Dr. Townsend and Dr. Thompson is, how do you envision this interrelationship? It clearly is not one-to-one. Some of the antagonists that work on the gastrin side really do not have a similar effect on the cell lines, and so what is your explanation for this seeming difference?

Second, they have so nicely shown that G-17, which is the active analog of a smaller portion of gastrin, has a calcium-releasing effect. And I am sure that they have fragments starting with G-1 to G-13 and pentagastrin, as well as probably a number of other antagonists to the smaller peptides; have you tried that? Is the role of gastrin in this particular situation merely a role of the longer chain link protecting the peptide from the destructive effects of proteases, or does it have some other effect?

And, finally, I suppose the easiest way to try this in humans would be to take population at risk like people with pernicious anemia or achlorhydria and give an antagonist over a long time. Do they have any estimate of what the latent period would be and how practical this would be as a clinical trial? This is really a landmark paper, and I enjoyed it very much.

DR. WALLACE P. RITCHIE, JR. (Philadelphia, Pennsylvania): President Ochsner, Secretary Scott Jones, I would like to thank Dr. Townsend very much for allowing me to review this manuscript because it does give me an opportunity to participate in this very nice two-paper mini-festschrift that they have organized for us today, and done very nicely, too. I must say I am a little surprised at being asked to discuss the paper because it is quite beyond my expertise in many respects. I am surprised but not embarrassed, because 30 years of observation in academic surgery have convinced me that total ignorance of a subject is no impediment whatsoever in discussing any subject at any length.

Today's presentation is another in a very fine, very intriguing series of studies in which this group has sought to characterize and define the effects of gastrointestinal hormones, particularly those with known trophic properties for normal gastrointestinal mucosa, on the growth of neoplasms of the gastrointestinal tract, both human and animal and both *in vivo* and *in vitro*. And today they have shown us — and this is for the first time, incidentally — that synthetic human gastrin G-17 stimulates growth of a human gastric adenocarcinoma through specific gastrin receptors by mechanisms that are linked to the mobilization of intercellular calcium but are quite independent of PI turnover and cyclic adenosine monophosphate production.

I have a few very brief questions, some of which are iterative, but I will ask them anyway. You have shown that receptors exist in the parent cell line in one of two clones. How universal do you think these findings would be if we looked at the whole world of gastric adenocarcinoma? Have you studied — I am sure you have — other human cell lines besides AGS? Have you characterized the gastrin receptor in AGS? Is it the same gastrin receptor as found in normal parietal cells in the proximal stomach? I suspect the answer is yes. I think you have demonstrated in at least one cell line, that is, the MC-26 mouse colon cancer, that responsiveness to gastrin wanes with time, with multiple passages of tumor cells over the long term, probably because of a reduction in the number of gastrin receptors in the tumor cells. Is this going to be the case here? I suspect it is not, but I think it is an important question because if in fact it were the case, it might impact on the potential for a gastrin receptor antagonist to act as an effective chemotherapeutic agent.

Finally, as with Dr. Fischer, I wonder if you would just comment on the implication of today's findings for the two clinical conditions that I can think of in which there is a strong association between neoplasia and hypergastrinemia. One has already been mentioned, that is, pernicious anemia. And the other is enterocromaffin cell-like hyperplasia, a consequence of profound hypochlorhydria induced by some of these wonderful anti-ulcer agents. It is a grand study, and I appreciate very much the opportunity to discuss it.

DR. COURTNEY M. TOWNSEND, JR. (Closing discussion): I would like to thank the discussants for their comments and their provocative questions. Dr. Bland and Dr. Fischer both asked why is there a biphasic response and why is it not always linked to the growth response and the calcium response apparently is not directly related. The answer basically is I do not know. We did the calcium studies, so far, in the parent cell line. We know that is a heterogenous population of cells. It contains cells that do and do not have gastrin receptors. Whether that explains in part, we do not know yet. We will continue the examination in other clones that have varying amounts of gastrin receptors to try to determine that.

We have not done any *in vivo* studies with this particular cell line using this analog. The analog is synthesized by our colleague John Martinez in Montpelier, France, and it is a dear compound. That is why we have not been able to completely evaluate the effects on all the clones that we have shown. We hope to do that. Other agents that might block the growth of the cells *in vivo* we have not studied yet. However, Mark Evers showed with another human gastric cancer cell line that grew in nude mice that inhibition of endogenous gastrin by the synthetic prostaglandin analog significantly inhibited the growth of another gastrin receptor–positive cell line.

The question that Dr. Fischer asked about the structure–function relationships, that is, using gastrin analogs of various lengths, is clearly one that we wish to pursue, but we have not done that yet.

In answer to both Dr. Fischer and Dr. Ritchie, clinical trials certainly would be intriguing to us. However, acquiring a large number of patients with pernicious anemia is difficult at best, and we have not embarked on any of those at this time.

Specifically, then, to answer some of Dr. Ritchie's questions, we have examined four different human gastric cancer cell lines. Three of the four have had gastrin receptors. One clearly does not, and does not respond to gastrin. I do not know what it would mean in the real world of gastric cancers. We are currently banking tissues in an attempt to conduct just such a survey. The characteristics of the gastrin receptor on this cell line have not completely been defined; we have gotten only preliminary results from our cross-linking studies to show that there are probably at least two different molecular forms of the gastrin receptor, and whether these will be the same or somewhat different, at least in one of the sub-forms, we do not know.

And, finally, you are absolutely right. We have previously shown that as tumor growth progresses in the mouse colon cancer cell line, responsiveness to gastrin and, in fact, the expression of gastrin receptors decreases. For these studies we use cells in the similar and short passage differences, about only two passage differences, and we have not examined that, but we plan to in the future. Thank you very much.

Cytokine Modulation of Na$^+$-dependent Glutamine Transport Across the Brush Border Membrane of Monolayers of Human Intestinal Caco-2 Cells

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Previous studies have demonstrated that Na$^+$-dependent brush border glutamine transport is diminished in septic patients. To examine the potential regulation of this decreased transport by endotoxin, cytokines, or glucocorticoids, the human intestinal Caco-2 cell line was studied *in vitro*. Na$^+$-dependent glutamine transport across the apical brush border membrane was assayed in confluent monolayers of differentiated cells that were 10 days old. Uptake of 50 μM glutamine was determined after a 12-hour incubation with varying doses (10 to 1000 U/mL) of tumor necrosis factor-α, interleukin-1, interleukin-6, interferon-Γ, and various combinations of these cytokines. Studies were also done in cells incubated with *E. coli* endotoxin (1 μg/mL) or dexamethasone (1 and 10 μM). Endotoxin, tumor necrosis factor, interleukin-1, and interleukin-6 alone and in combination did not significantly reduce Na$^+$-dependent glutamine transport across the brush border of Caco-2 cells. Dexamethasone decreased glutamine transport by 20%, but this decrease was not apparent for 48 hours. Interferon consistently decreased glutamine transport by 30%; this was due to a reduction in carrier maximal transport velocity (3427 ± 783 pmol/mg protein/minute in controls *versus* 2279 ± 411 in interferon, $p < 0.05$) rather than a change in Km (276 ± 29 μM in controls *versus* 333 ± 74 in interferon, p = not significant). The combination of interferon + dexamethasone + tumor necrosis factor + interleukin-1 resulted in a 38% decrease in transport activity. Cytokines and glucocorticoids may work independently and synergistically in regulating Na$^+$-dependent brush border glutamine transport in human intestinal cells. Whether these signal molecules play a central role in the cause of the diminished brush border glutamine transport that occurs in septic patients requires further study.

THE SMALL INTESTINE occupies a central role in the absorption of ingested nutrients. Luminal amino acids are taken up by the brush border of intestinal epithelial cells by a variety of previously described transport systems.[1] Uptake of most amino acids is mediated principally by carriers that require sodium for transport and thus have been called sodium-symport systems. These transport processes require energy to maintain ionic gradients and to synthesize transport proteins. In the case of enterocytes, replicating cells with a rapid turnover, the amino acid glutamine (GLN) is a key fuel as well as a precursor for nucleotide biosynthesis.[2,3] The small intestine plays an important role in regulating GLN homeostasis in normal and catabolic states, and the transport of GLN by gut epithelial cells has been the subject of considerable recent study.[2,4–6]

We recently demonstrated that transport of GLN across the brush border membrane of both the jejunum and ileum is markedly decreased in septic patients.[5] Kinetic analysis of these data demonstrated Na$^+$-dependent GLN transport across the brush border membrane to occur through a single saturable high-affinity system. The decrease in transport in the septic patients was due to a decrease in carrier maximal transport velocity, consistent with a decrease in number of active carriers in the apical brush border membrane. To study the regulation of transport in intestinal epithelial cells, independent of cell–cell interactions and changes in the microcirculation, investigators have attempted to establish primary cultures of human intestinal cells. Unfortunately, these attempts have not been successful. Several attempts have also been made to study amino acid transport in cell suspensions, but the long-term viability, differentiation status of the various cells that are harvested, and morphologic polarization of isolated enterocytes prevent direct comparison with absorptive events at the apical surface of the small intestinal brush border *in vivo*.

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Recently, we characterized sodium-dependent GLN transport in the brush border membrane of human intestinal Caco-2 cells.[7] We demonstrated that Na^+-dependent GLN transport occurs predominantly through a high-affinity carrier (System B) that has kinetic parameters and an inhibition profile similar to that present in brush border membrane vesicles prepared from normal human jejunum.[8] Caco-2 is an established intestinal epithelial cell line from a human colon adenocarcinoma.[9-11] Caco-2 cells are the most relevant *in vitro* model for studies related to the regulation of substrate transport by small intestinal cells. These cells provide an excellent *in vitro* model that is directly analogous to the events of development in the small intestine; subconfluent cells are morphologically and biochemically equivalent to nondifferentiated crypt cells, whereas the differentiated confluent monolayer displays nearly all of the characteristics of mature differentiated enterocytes in epithelial layers.[9,10,12-14]

Because Caco-2 cells provide a useful model for the study of the regulation of amino acid transport by small intestinal cells, the purpose of this investigation was to study the effects of endotoxin, various cytokines, and dexamethasone on apical brush border GLN transport in confluent monolayers of differentiated cells.

METHODS

Reagents and Chemicals

All chemicals and reagents used were of analytical quality and were purchased from Sigma (St. Louis, MO). Radiolabeled L-GLN was purchased from Amersham (Arlington Heights, IL).

Caco-2 Cell Culture

The human colon adenocarcinoma established cell line Caco-2 was obtained from American Type Culture Collection (Rockville, MD, ATCC No. HTB 37). This cell line undergoes enterocytic differentiation in culture characterized by a polarization of the cell layer with the formation of domes and an apical brush border that contains brush border enzymes.[9,15] Morphologically, the cells develop desmosomes and tight junctions once they reach confluency and become impermeable to water-soluble fluid-phase markers. Cells were routinely grown in 60- × 15-mm Falcon plastic tissue culture dishes in 2 mL of Dulbecco's Modified Eagle Medium containing 25 mM glucose, 25 mM HEPES, and supplemented with 10% fetal bovine serum, 1% nonessential amino acids, 1% GLN, penicillin (100 IU/mL), and streptomycin (100 μg/ml). All culture reagents were from Gibco (Grand Island, NY). Caco-2 cells were grown at 37 C in a humidified atmosphere of 10% CO_2–90% air. The medium was changed 24 hours after subculturing, then subsequently changed daily. For subculturing, the confluent cells were dispersed by a treatment for 5 minutes with isotonic Ca^{2}+-free phosphate-buffered saline (pH 7.4, 37 C) containing 0.25% trypsin and 0.3% ethylenediaminetetra-acetic acid. The dispersed cells were sedimented in a sterile conical centrifuge tube at 1000*g* for 1 minute, and the supernantant was removed. Then culture medium (see above) was added to resuspend the cells to a seeding density of 1.93 × 10^5 cells/mL (measured using a hemocytometer). Finally, 2 mL of this cell suspension was added to new culture dishes such that each 35-mm dish was seeded with 3.85 × 10^5 cells; cells were subcultures with a split ratio of 3:1. All of the above procedures were done under sterile conditions using filter-sterilized solutions (0.2 μm Gelman membrane filter, Gelman Sciences, Ann Arbor, MI) in a laminar air-flow hood. The cultures were inspected daily (using phase contrast microscopy) to monitor monolayer confluency status and to ensure normal culture health (dome formation, absence of contamination, etc.).

At this point, cells were seeded at a density of ~ 60,000 cells/cm^3 in each well of a 24-well (Costar, Costar Corp., Cambridge, MA) tray. The cells reached confluence in 5 days; the culture medium was changed as necessary, at least every 1 to 2 days. The cells were studied 4 to 6 days later, 9 to 10 days after plating the cells, at which time the cells exhibited the enterocytic features described above.

Cytokines

Nine to 10 days after plating cells in 24-well trays, various cytokines, alone and in combination, were added to the culture medium at concentrations of 10, 100, or 1000 units/mL. The cytokines studied were tumor necrosis factor-α (TNF, a gift from Dr. Patricia Olsen, Chiron Corp, Emoryville, CA), interleukin-1 (IL-1, a gift from Dr. Peter Lomedico, Hoffman-LaRoche Corp, Nutley, NJ), interleukin-6 (IL-6, a gift from Dr. Lyle Moldawer, Department of Surgey, Cornell Medial School, New York, NY), and interferon-Γ (IFN, Sigma). Additionally, trays of cells were incubated with endotoxin (*Escherichia coli* 0127:B8, Lot 76F4053, Sigma, 1 μg/ml) or dexamethasone (1 and 10 μM). In all studies, control wells were from the same tray as the cells treated with the aforementioned compounds. These potential regulators were dissolved in sterile water at appropriate concentrations such that when 25 μL solution was added to each milliliter of culture medium, the desired final concentration was obtained. Controls cells were treated with 25 μL of vehicle.

Transport of Radioactively Labeled Glutamine by Caco-2 Cell Monolayers

All transport studies were done at pH 7.4 at various timepoints (2, 4, 8, and 12 hours) after addition of the various compounds mentioned above. Cells incubated in the presence of dexamethasone were also studied after 24 and 48 hours of incubation. Transport studies were done in 24-well cluster trays (Corning Glassworks, Corning, New York). Transport of radioactively labeled GLN [^{3}H-GLN], Amersham) by cells was assayed by a modification of the method described originally by Gazzola et al[16] that we use regularly in our laboratory.[17] The lids to the 24-well cluster trays were modified so that they contained either 12- × 75-mm plastic test tubes or Beem embedding capsules (00, PolySciences, Warrington, PA). These lids allow simultaneous transfer of either 2 mL (warm or cold washes) or 0.25 mL (uptake mixture) medium, respectively, to each of the 24 wells, by placing the bottom of the tray, to which the cells are attached, upside down on either of the modified lids, and then rapidly inverting the entire unit.

To allow for a partial depletion of intracellular and extracellular amino acids, the original media was discarded and replaced with 0.5 mL per well of sodium Krebs-Ringers Bicarbonate buffer (37 C) and incubated under 10% CO$_2$ at 37°C for 60 minutes. At the end of the 60-minute period the sodium Krebs-Ringers Bicarbonate buffer was removed and the wells were rinsed with 0.5 mL of choline Krebs-Ringers Phosphate Buffer (Chol KRP, 37 C) and discarded. This was followed by another 0.5 mL Chol KRP in which the cells were incubated for 5 minutes in a 37 C waterbath (this process removes extracellular sodium before the transport assays). After removal of the depletion buffer, the transport assay was initiated by transferring 0.25 mL of the uptake medium at 37 C to all 24 wells. The uptake buffers were prepared from either sodium Krebs-Ringers Phosphate or Chol KRP containing the radioactively labeled amino acid (^{3}H-GLN, 6 μCi/mL) as well as the appropriate concentration of unlabeled GLN. Transport measurements done using the Chol KRP buffer allowed us to calculate sodium-independent GLN transport by Caco-2 monolayers. The transport reaction was terminated at the appropriate time by rapidly inverting the cluster tray over a dish pan to remove the uptake mixture, followed by the immediate rinsing of cells with ice-cold Chol KRP four times (2 mL per well per rinse). The trays were placed upside down on absorbent paper and allowed to stand for 20 to 30 minutes. The cells in each well were solubilized by the addition of 200 μL of 0.2% sodium dodecyl sulfate in 0.2 N NaOH for 30 minutes at 22°C. At the end of the incubation period, 100-μL aliquots of the cell suspension were neutralized with 100 μL 0.2 N HCl and transferred to scintillation vials for determination of the radioactivity. The remaining 100 μL in each well was used to assay the protein content by the Lowry method.[18] Radioactivity was determined by liquid scintillation counting, and the transported (intracellular) ^{3}H was calculated. Transport velocities were calculated from radioactive counts and protein values using a PASCAL computer program. A schematic of the technique used to assay GLN transport is shown in Figure 1.

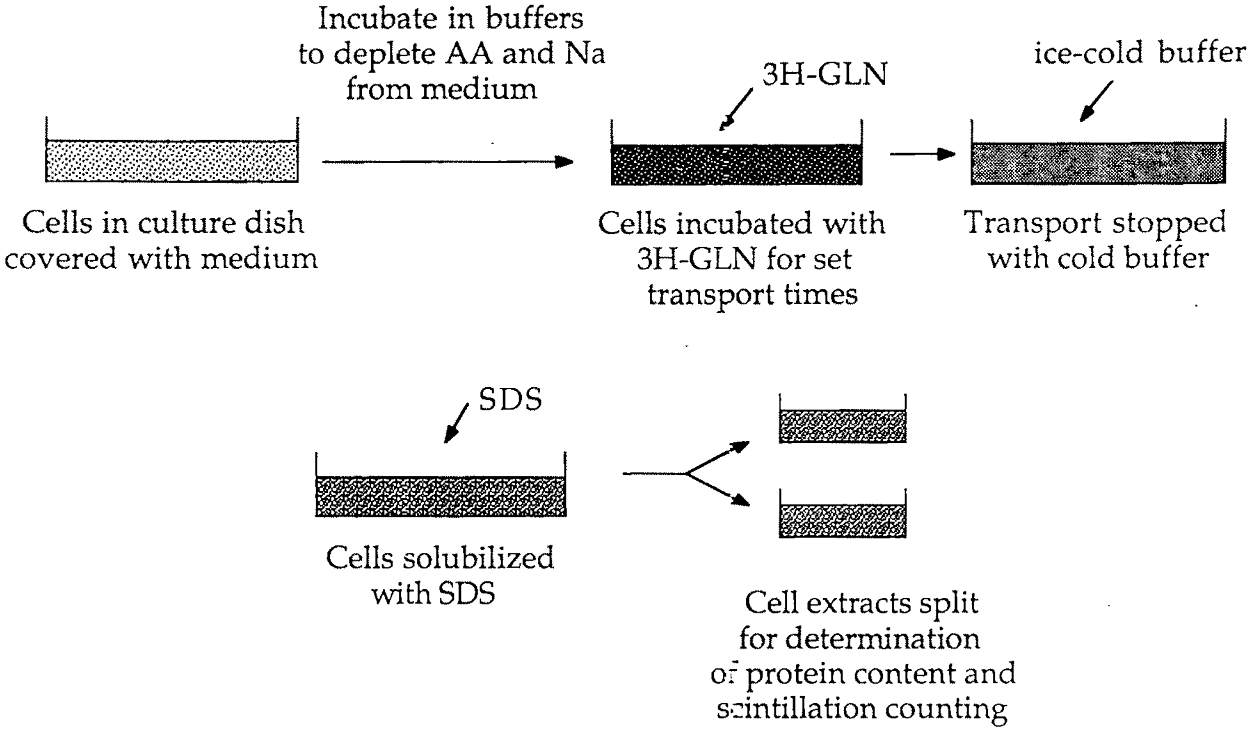

FIG. 1. A technique for measuring glutamine transport in confluent Caco-2 monolayers.

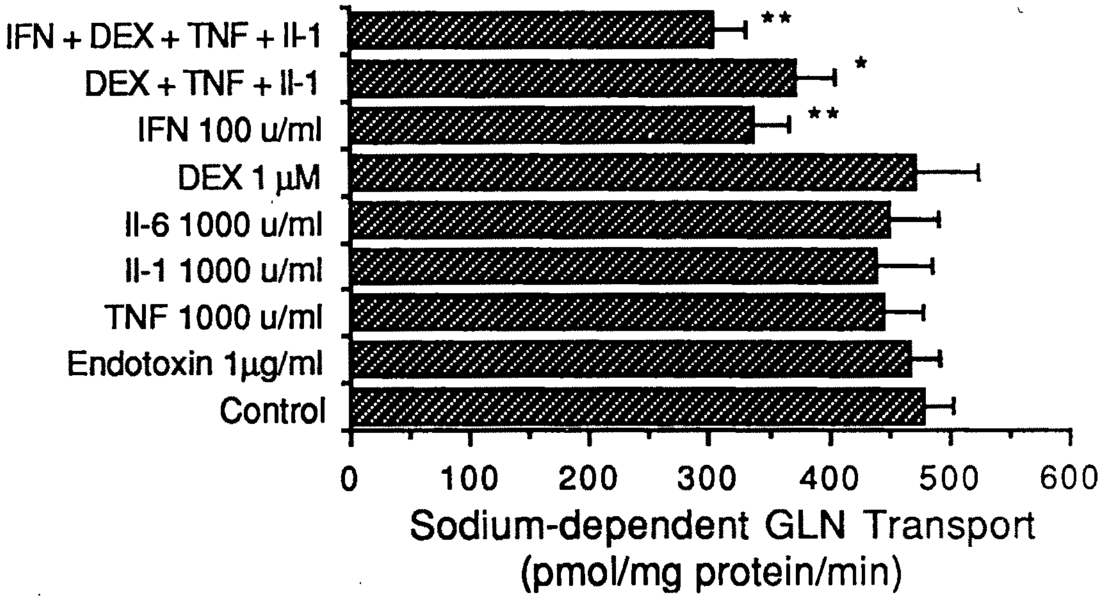

FIG. 2. Effects of endotoxin, various cytokines, and dexamethasone on Na^+-dependent glutamine transport in 9- to 10-day-old Caco-2 cell monolayers. Cells were grown and glutamine transport was assayed as described in Methods. The data shown are for cells incubated with sterile water (controls) or the indicated compounds for 12 hr before transport. The results are mean ± SEM of three to six separate experiments. $^*p < 0.05$. $^{**}p < 0.01$ *vs.* control.

Statistical Analysis

All data are reported as mean ± standard error. Each of the experiments was conducted independently, and each measurement was obtained in triplicate. The data in the figures represent the mean ± the standard error of the mean of three to six separate experiments. Transport velocities are expressed in picomoles of GLN per milligram cell protein per minute. Data were analyzed using analysis of variance or Student's t test. A p value less than 0.05 was considered to be statistically significant.

Results

Effects of Endotoxin and Cytokines on ^3H-GLN Uptake

Confluent Caco-2 cell monolayers were incubated with the various compounds shown in Figure 2 for up to 12 hours, and Na^+-dependent GLN transport was measured. The sodium-dependent fraction of GLN entry, determined by subtracting the velocity in the sodium-free media from that obtained in the sodium-containing media, is a saturable function of GLN concentration. Uptake was found to be linear for at least 15 minutes, and the rate of uptake in the sodium-free media represented more than 80% of the total uptake at all time points. On the basis of these results, we used an incubation time of 2 minutes to insure that transport assays were at initial rates for our remaining experiments, and we confine our results reported here to Na^+-dependent GLN transport. All further experiments were carried out with a final GLN concentration of 50 μM.

Endotoxin, TNF, IL-1, and IL-6 had no effect on Na^+-dependent brush border GLN transport when added to the culture medium alone. Data from the 12-hour timepoint are shown in Figure 2. A representative timecourse for TNF is shown in Figure 3. Lower concentrations of cytokines also had no effect on uptake (data not shown). Only IFN alone consistently resulted in a 30% decrease in Na^+-dependent GLN transport. An effect of IFN was observed as early as 4 hours, but was not statistically significant until the 12-hour timepoint. Small concentrations

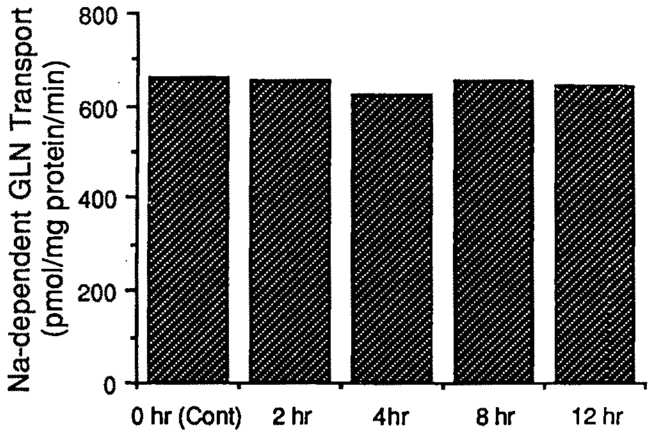

FIG. 3. Representative plot of Na^+-dependent brush border glutamine transport in cells incubated with TNF (1000 U/mL) for varying periods. Multiple experiments (>3) were done in separately seeded generations of cells that showed that incubation with TNF, IL-1, or IL-6 at several doses (10, 100, and 1000 U/mL) for varying periods (2–12 hr) had no effect on glutamine transport.

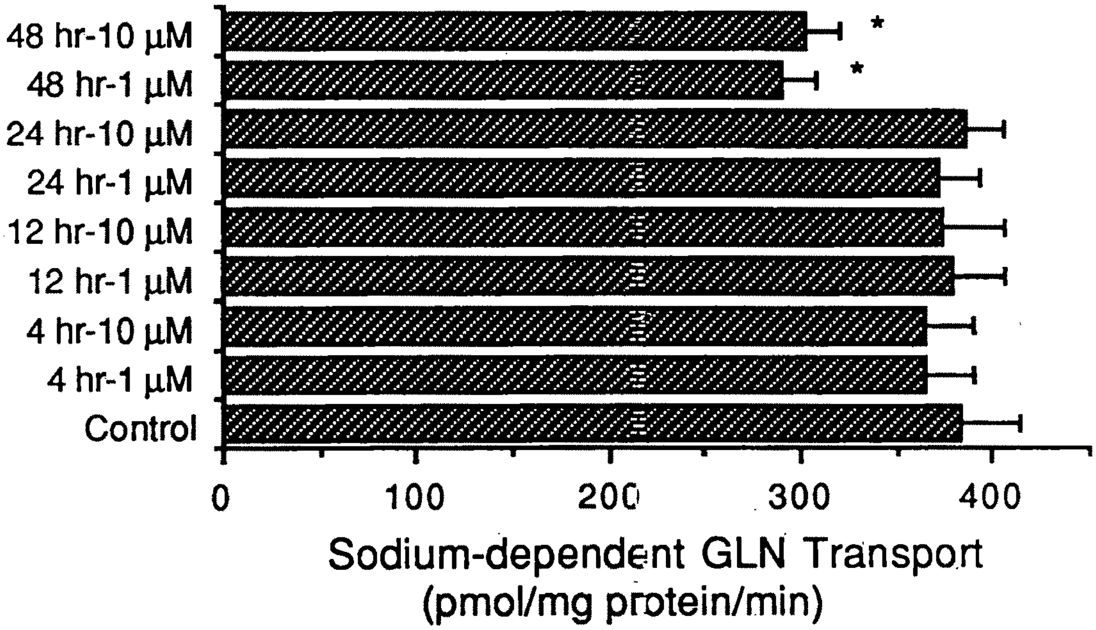

FIG. 4. Effects of dexamethasone on Na$^+$-dependent glutamine transport in Caco-2 cells. *$p < 0.05$.

of IFN were as effective as high concentrations of IFN in diminishing GLN transport (Figure 4). The combination of TNF, IL-1, and dexamethasone decreased Na$^+$-dependent GLN transport by 21%. When a cocktail of IFN (100 U/mL), dexamethasone (1 μM), TNF (1000 U/mL), and IL-1 (1000 U/mL) was added to confluent monolayers, a 38% decrease in Na$^+$-dependent GLN transport was observed (Fig. 2).

Effects of Dexamethasone on Na$^+$-dependent Glutamine Transport by Caco-2 Cells

Similar studies were done in cells incubated with dexamethasone (1 and 10 μM) for varying periods (4, 12, 24, 48 hours). The results demonstrated that dexamethasone had no effect on GLN transport across the brush border of confluent Caco-2 monolayers except at the 48-hour timepoint, when transport in dexamethasone-treated cells was diminished by 20% (Fig. 5). Thus, cytokines (especially IFN) may exert relatively acute effects on GLN transport, whereas glucocorticoid effects are moderate and occur in a more chronic fashion.

Transport as a Function of Glutamine Concentration/Kinetics of ^{3}H-GLN Uptake

Because IFN consistently caused a 30% to 40% decrease in Na$^+$-dependent GLN transport, we examined the effects of IFN on transport kinetics. Glutamine uptake by Caco-2 cells was measured at various GLN concentrations ranging from 50 μM to 5 mM in the presence of both Na$^+$ and choline gradients. The kinetic parameters of the Na$^+$-dependent transporter in control and IFN-treated (100 U/mL) were determined using the following equation:

$$J^{total} = J^{Na\text{-}dep} + J^{Na\text{-}indep} + J^{D} \qquad (A)$$

where J^{total} refers to total uptake in the presence of Na$^+$, $J^{Na\text{-}dep}$ refers to Na$^+$-dependent carrier mediated uptake, $J^{Na\text{-}indep}$ denotes Na$^+$-independent carrier-mediated uptake, and J^D refers to diffusional uptake. Uptake in the absence of sodium (in the presence of choline) is summarized by the following equation:

$$J^{Chol} = J^{Na\text{-}indep} + J^{D} \qquad (B)$$

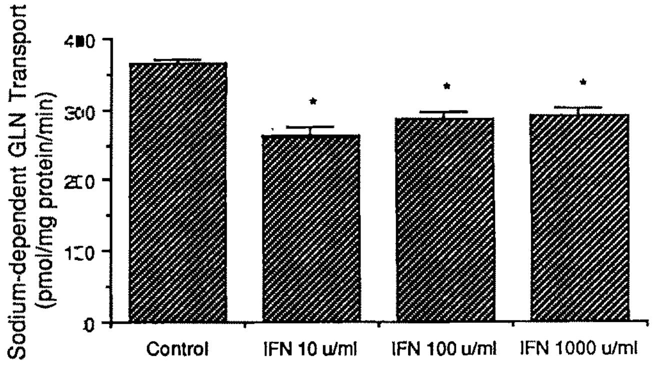

FIG. 5. Effects of IFN on Na$^+$-dependent brush border glutamine transport in 9- to 10-day-old Caco-2 cell monolayers. Data are the mean ± SEM of four separate experiments. The data shown are for cells incubated with various doses of IFN for 12 hr. *$p < 0.01$. IFN decreased GLN transport at earlier time points, but this decrease did not reach statistical significance.

The net Na$^+$-dependent carrier-mediated fraction of uptake was determined by subtracting equation (b) from equation (a). A saturation plot (Na$^+$-dependent GLN uptake velocity *versus* [GLN]) for control and IFN-treated cells is shown in Figure 6. When the results were plotted as $J^{Na\text{-}dep}$ *versus* $J^{Na\text{-}dep}$/[GLN], they demonstrated that the data could be fitted by a single linear regression line. This indicated that GLN uptake by Caco-2 cells occurs predominantly through a single saturable Na$^+$-dependent transporter, similar to what we had previously reported.[7] A representative Eadie-Hofstee plot for control and IFN-treated cells is shown in Figure 7. When data from four separate kinetic studies were averaged, it was apparent that the decrease in transport we observed in Figures 4 and 6 was due to a 33% reduction in carrier maximal transport velocity (3427 ± 783 pmol/mg protein/minute in controls *versus* 2279 ± 411 in IFN, $p < 0.05$, paired t test) rather than a change in Km (276 ± 29 μM in controls *versus* 333 ± 74 in IFN, p = not significant).

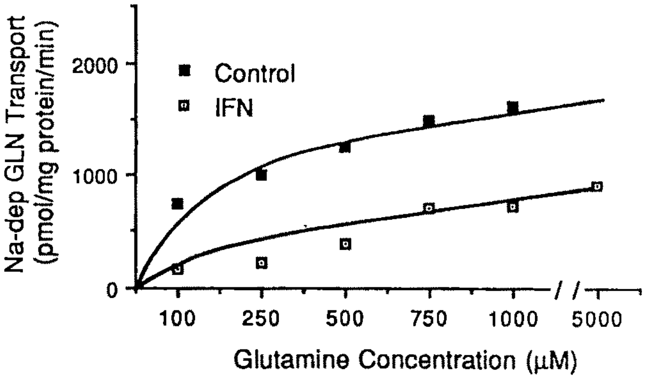

FIG. 6. Saturation plot of Na$^+$-dependent glutamine transport in Caco-2 cell monolayers. Transport was assayed 12 hr after IFN or sterile water (control) was added to the cell culture medium. Transport in IFN-treated cells was decreased compared with control cells at all glutamine concentrations.

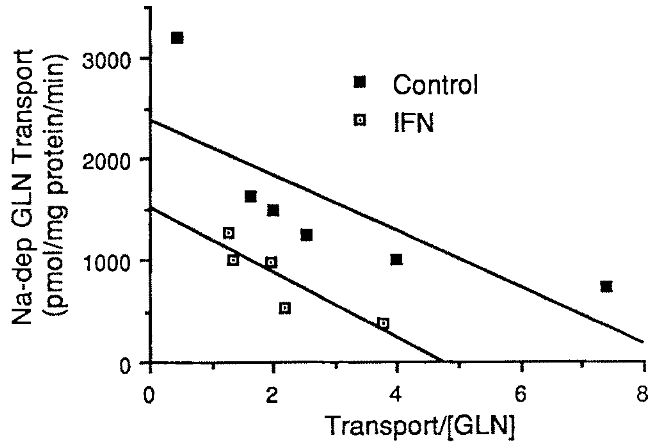

FIG. 7. Eadie–Hofstee plot of Na$^+$-dependent glutamine uptake kinetics in control ($r = 0.78$) and IFN-treated (100 U/mL) ($r = 0.88$) confluent Caco-2 monolayers. Transport velocity was plotted as a function of velocity/(glutamine). A single saturable transporter system was present in both control and IFN-treated cells as shown by single straight lines. A representative plot is shown. Data from four different experiments (from separately seeded Caco-2 cell generations) showed a 33% decrease in V_{max} (3426 ± 783 pmol/mg protein/min in controls *vs.* 2279 ± 411 in IFN, $p < 0.05$, paired t test). IFN did not alter transporter affinity (Km = 276 ± 29 in controls *vs.* 333 ± 74 in IFN, p = NS).

Discussion

The effects of endotoxin, various cytokines, and dexamethasone on Na$^+$-dependent GLN transport across the brush border membrane of differentiated confluent Caco-2 cells were studied in the hopes of gaining further insight into the metabolic role the small intestinal epithelial cell plays in intestinal GLN uptake during septic states. Our interest in studying the potential regulation of brush border GLN transport by these compounds was stimulated by previous studies that showed that intestinal GLN transport was diminished in septic patients and in endotoxin-treated rats.[5] We focused on the 12-hour timepoint because our previous studies showed a clearcut decrease in carrier maximal transport velocity 12 hours after a single dose of *E. coli* endotoxin. Interestingly, in the rat, a biphasic response is observed characterized by an early (4 hours after endotoxin treatment) increase in GLN transport before the 12-hour decrease in uptake. In the investigations reported in this manuscript, we did not observe an increase in GLN transport at any timepoint with any of the mediators we investigated. Thus, in the current study, cytokines could account for some but not all of the changes we previously observed in our animal studies. Most likely other factors, such as hypoxia and changes in the local pH environment, also play a role in regulating GLN uptake from the gut lumen. Endotoxin also might "injure" the Na$^+$ K$^+$ adenosine triphosphatase enzyme, which could decrease transport under certain circumstances because many amino acid transporter systems are energized by Na$^+$ electrochemical gradients. Nonetheless, our experiments demonstrate that cytokines and glucocorticoids may work independently and synergistically in regulating Na$^+$-dependent brush border GLN transport across the brush border. Previous studies using brush border membrane vesicles from the glucocorticoid-treated dog are consistent with our observations.[19]

To study GLN transport in isolated human enterocytic cells, we used confluent differentiated monolayers of Caco-2 cells. Before the current study, studies designed to examine the regulation of GLN transport across the brush border have been done in brush border membrane vesicles prepared from animals and patients.[4,5] The advantage of membrane vesicles is that they reflect transport *in vivo.* Vesicles also allow us to study transport separate from cellular metabolism. Transport activity in vesicles, however, is not examined independent of other influences such as cell–cell interactions and changes in the microcirculation. Consequently, investigators have attempted to use cultured intestinal epithelial cells to examine various physiologic events because the regulation of such events can be studied separate from endocrine and paracrine factors. Although a variety of methods have been used to prepare isolated enterocytes, the viability of these cells has proven to be short-lived, and attempts at long term cell culture have been unsuccessful. The advantage of differentiated Caco-2 cells in monolayer culture is that they can be maintained in a nonreplicating state for a period long enough to allow us to study regulatory events that take at least several hours to occur.

Caco-2 is an established intestinal epithelial cell line from a human colon adenocarcinoma.[9,10] The Caco-2 apical membranes express Na^+-coupled glucose cotransporters, Na^+/phosphate cotransporters, and on differentiating, they express greater amounts of brush border digestive enzymes such as sucrase-isomaltase, maltase, lactase, trehalase, gamma-glutamyltranspeptidase, and alkaline phosphatase.[20–25] A rapidly growing literature substantiates the favorable comparison of Caco-2 cultures with normal intestinal cells. Postconfluent Caco-2 cells synthesize and secrete lipoprotein and produce mRNAs for growth factors and receptors.[13] Thus, the Caco-2 cell provide an excellent tool for the study of cytoplasmic amino acid transport in intact cells. The kinetic parameters of the GLN transporter that we described in confluent Caco-2 monolayers are similar to those we observed in brush border membrane vesicles from normal human small intestine.[5]

Cytokines are polypeptide molecules produced by a variety of cells in response to bacteremia and endotoxemia. They are responsible for many of the metabolic responses that occur during severe infection. In addition, they appear to be important regulators of GLN transport in many different tissues. For example, both TNF and IL-1 stimulate GLN transport by endothelial cells.[26] Glutamine transport in hepatocyte plasma membrane vesicles from TNF-treated- or IL-1–treated rats is increased 50% to 80% (Souba, unpublished observations). Conversely, TNF causes a 45% decrease in System ASC-mediated GLN transport by human fibroblasts.[27] The current investigations indicate that cytokines also regulate GLN transport in the intestine. Of key significance is that endotoxin did not alter Na^+-dependent GLN transport across the brush border of Caco-2 cells at any timepoint. Thus, the decrease in luminal GLN transport we observed in septic patients and endotoxin-treated rats was probably not due directly to endotoxin, but rather was caused other signals produced as a consequence of endotoxemia. In the current study, only IFN alone resulted in a decrease in transport; combination treatment also had a slight effect. In the absence of IFN, this required dexamethasone, consistent with a permissive effect exerted by glucocorticoids. Previous investigators have demonstrated that glucocorticoids can enhance cytokine activity by increasing receptor expression on the cell membrane.[28]

Our observation that IFN results in a significant decrease in sodium-dependent brush border GLN transport by confluent Caco-2 monolayers is important because IFN is generally viewed as as cytokine that has immunologic rather than metabolic effects. This cytokine increases respiratory burst activity[29] and killing activity of host macrophages [30] and can be produced by circulating human lymphocytes.[31] To our knowledge this is the first report that shows that IFN modulates the activity of an amino acid transporter. Our results indicate that IFN decreases GLN transport by decreasing the maximal transport velocity of the carrier. This is consistent with a decrease in the number of functional transport molecules in the brush border membrane. This may occur secondary to a decrease in the rate of *de novo* carrier biosynthesis, an increase in the rate of carrier breakdown, or from the synthesis of some inhibitory protein that blocks transporter function. As mentioned earlier, the specific role that cytokines play in the cause of the diminished brush border GLN transport that occurs in septic patients requires further study.

Various distinct amino acid transport systems have been defined on the basis of their amino acid selectivities and physicochemical properties,[1] each system presumably relating to a discrete putative membrane-bound transporter protein. None of these carrier proteins has been identified or isolated, so investigators have relied on kinetic and competitive-inhibition analyses to define and characterize the individual systems. The uptake of GLN as well as other neutral amino acids across mammalian cytoplasmic membranes have been categorized according to substrate specificity, effects of external pH changes, sodium-dependent and independent systems, and sensitivity to hormones. On the brush border membrane of the small intestine, a neutral brush border system (system B) has been characterized[7,32,33] that appears to be distinctly different from other more ubiquitous sodium-dependent systems. The neutral brush border carrier transports most neutral amino acids, including alanine, cysteine, and GLN.

Characterization of carrier-mediated substrate transport across cell membranes includes determining the maximal transport velocity and the Michaelis constant (Km) of the specific transporter. Although most amino acid carriers transport several different amino acids, the kinetic parameters for each amino acid transported by the same carrier protein should be quite similar. In general, the transport activity of a specific carrier can increase or decrease in two principal ways: either the affinity of the transporter for its substrate changes or the number of active transporters in the cell membrane changes. Conceptually a decrease in transporter affinity occurs because the conformation (tertiary structure) of the carrier protein (or possibly an adjacent comodulator protein) changes such that the substrate binds less readily (less rapidly, less tightly) to its binding site on the transporter. Presumably such a change would result in fewer molecules translocated into the cell in a given period.

The second general way that the rate of GLN transport across the brush border could be diminished is to decrease the number of transporter proteins in the cell membrane. As best we know, this usually involves a decrease in *de novo* protein synthesis, often of the carrier itself. Alternatively, a regulatory protein could be synthesized that represses transporters that are active. More exact elucidation of these mechanisms will be possible when the specific genes encoding for the various carrier proteins are cloned.

Several questions arise. Why should system B transporters in the brush border be reduced in number if GLN is so important to the enterocyte, especially in times of critical illness? Is this response adaptive or due to a generalized impairment in protein synthesis from cell injury? We think the response is adaptive (unless the insult is so severe that it results in cell death) for several reasons. First, at a time when transport activity is diminished, the activity of other vital intracellular proteins is likely to be increased. Second, vesicles from endotoxin-treated rats exhibit a biphasic response to endotoxin: an early stimulation of GLN transport followed by a decrease in transport. Possibly, the cell is prioritizing protein synthesis at a time when substrate precursors are limited. Moreover, in the overall scheme of organ hierarchy, perhaps the gut becomes subservient to the liver, which becomes the principal organ of GLN uptake in sepsis.

Previous studies in our laboratory have demonstrated that the small intestine plays a key role in interorgan GLN flow in normal and catabolic disease states. Intestinal uptake of GLN from both the lumen and bloodstream is decreased in septic patients and in endotoxin-treated rats.[5,6] In the current study, Caco-2 confluent monolayers were used to study the regulation of brush border GLN transport *in vitro*. The consequences of the decrease in GLN transport that occurs in Caco-2 cells incubated with cytokines is unknown. Similar cytokine-mediated decreases in GLN transport are observed in rat intestinal crypt cells (Souba, unpublished observations). Intestinal uptake of circulating GLN is also decreased *in vivo* in the IL-1–treated rat, suggesting that cytokines may also modulate basolateral membrane GLN transport. We have begun transport studies in Caco-2 cells grown on millipore filters that allow us to study basolateral membrane transport *in vitro*. Several *in vivo* studies suggest that a persistent decrease in GLN availability is detrimental to the intestinal mucosa. These studies are consistent with an absolute GLN requirement by the enterocytes.

The intestinal epithelium is a rapidly renewing tissue that exhibits high rates of cell replication. Undifferentiated crypt cells arise from stem cells, and on starting rapid proliferation, the increased protein synthesis rate results in an increased demand for amino acids. Once the cells migrate up out of the crypt zone to the villus tip, they become differentiated nondividing enterocytes whose primary function has traditionally been viewed to be one of digestion and absorption. It now apparent that the gut mucosa also occupies a central role in the response to injury and infection. Although most of the research in this area has been directed to studying the gut mucosal barrier, the work presented here further substantiates the important role the gut occupies as a nitrogen processing station. How intestinal metabolism influences gut structure and function is still unclear, but the current studies emphasize the need to continue such investigations.

Acknowledgment

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DISCUSSION

DR. NEAL GARRISON (Louisville, Kentucky): President Ochsner, Secretary Jones, Members and Guests, I rise to compliment Drs. Souba and Copeland on an outstanding and very sophisticated piece of work, most especially Dr. Copeland for the foresight to bring the slides with him in preparation for this talk. It is one of a continuing series of investigations into the metabolism of glutamine that has come from the laboratories of the University of Florida. Dr. Souba provided me with a finished copy of this work along with several background reprints, which allowed me to do my homework and helped me tremendously in understanding this phenomenon.

The focus of this work is to outline where the utilization of glutamine is depressed or altered during sepsis or stress states and whether this depression can be circumvented and, thus, beneficial to the patient. I have two questions for the authors: In view of the fact that during stress there is a marked reduction in mucosal blood flow during sepsis with a presumed state of ischemia produced, what effect does altered pH or reduced energy production secondary to oxygen deprivation have on this process of glutamine metabolism? I assume it is an energy-driven overall system, the metabolism of glutamine, and thus, in tissue culture the local environment usually is held constant.

My second question is, what is the evidence that cytokines that you used in these experiments are directly exposed to mucosal cells in the normal anatomic situation? It is my understanding that most of these molecules work through receptors on endothelial cells or other white blood cells but not necessarily directly on functional mucosal cells. I thank the Association for the privilege of the floor.

DR. JOSEF FISCHER (Cincinnati, Ohio): President Ochsner, Secretary Jones, Members and Guests, I apologize for rising again. I did get the manuscript several weeks ago and did have the opportunity to review some of this excellent work that has been presented in the past. In the continuing elucidation of some of the changes in sepsis and glutamine, Dr. Souba and Dr. Copeland have pointed out that there are really some profound changes that take place in the gut mucosa. In this case, in dealing with glutamine, which is a major energy source physiologically, the direction is decreased. That is, glutamine uptake is decreased. And that is in a little bit of a contradistinction to what happens elsewhere in the gut, such as increased protein synthesis and, presumably, the increased protein synthesis that goes on in the liver, which is partially influenced in the gut.

I am under some strictures in my discussion. Dr. Copeland pointed out very clearly to me when he gave me the paper and told me Dr. Souba was not going to be here, that I am not to ask any questions about science, just the political implications of his findings. However, I really cannot resist. So, Ted, I will hang a couple of fast balls over the plate. First of all, this group is having the same difficulty that everybody else has who works with the small intestine. It is really impossible to get the cells that you isolate *in vivo* to survive for more than 60 minutes, and it is really difficult to get the cells to survive in a way that you are convinced that they actually can do things you want them to after 30 of those minutes. So they have to use, as we do, the CACO-2 culture, which is a good model for the cell as far as it goes. The problem with the CACO-2 culture is the actual overall model. You have to add the material to the well. And they pointed out this difficulty very nicely in the manuscript by showing that although endotoxin, as they presented last year, works very well, if you add endotoxin to the well, it does not do anything. So, therefore, I think you would have to add a word of caution to some of the conclusions not based on the excellence of the work, which is really first class, but on the model, as to whether or not you can conclude that the cytokines either do or do not have much to do with what is happening. I think one could accept interferon as having an effect on the decreased glutamine transport, but I think one should exercise a note of caution before really concluding that interleukin-1, for example, or interleukin-6, do not have anything to do with it. Because one then would have to show, as they did with endotoxin, that you inject the interleukin-1 or the interleukin-6 or the tumor necrosis factor into a rat and substitute the rat serum for the fetal calf serum, 10% for example, and then see what happens. So my first question is, in fact, have you done this?

Another way of approaching this issue is to use a combination of effects *in vivo,* which they have done *in vitro.* So my second question is, have they carried out some of the combinations such as interleukin-1 and tumor necrosis factor in the intact rat and then tried to transpose the serum? The third way of approaching it actually in the well might be to use an interleukin-1 receptor antagonist, which are now available, that might conceivably affect the glutamine transport *in vitro* despite the fact that interleukin-1 does not have an effect *in vitro.*

And, finally, I am having a little bit of a problem really correlating all of these changes in sepsis. I will accept the fact that glutamine transport is decreased *in vivo* and, seemingly, *in vitro* in a model that is similar. But there are some other things that go in the gut that are energy-requiring, like protein synthesis, which is increased dramatically. In our laboratory we have shown that one of the things the gut appears to be doing is synthesizing tremendous amounts of things like vasoactive intestinal polypeptide and PYY and releasing them, presumably in portal (ph) circulation, which may be a signal to the liver. We know that glutamine really is an essential energy source for this particular process. Your block of glutamine with DON synthesis decreases. When you substitute other energy sources like acetoacetate, it increases again. How do you put this all together? There is a biphasic response you showed last year with endotoxin in which glutamine transport first increases, then decreases. Is this a way in which this could be reconciled? I really enjoyed this whole series of papers very much and will look forward to what, undoubtedly, will be a greater presentation with Dr. Souba closing. Thank you.

DR. J. RAYMOND FLETCHER (Mobile, Alabama): Thank you, Dr. Ochsner, Dr. Jones, Guests, Members of the Southern Surgical. I have to congratulate Drs. Souba and Copeland for such an elegant study, designed to determine the mechanisms of decreased uptake of glutamine in the small intestine in septic patients. The authors used cultured endothelial cells exposed to a variety of mediators. It was presented very nicely by Dr. Copeland.

It is well known that endotoxin in animals and humans at much lower doses than used in this study elicit the release of many mediators, including interleukin-1, tumor necrosis factor, the prostaglandins, and platelet-activating factor, all of which have potent effects on the gastrointestinal tract; platelet-activating factor, perhaps, having the most profound changes. In the current study, the authors demonstrate no effect of endotoxin on this glutamine uptake in these cells, a surprising finding with the duration of the experiment, because endotoxin is known to release tumor necrosis factor and interleukin-1 *in vivo.*

There are a few questions that I would like to ask the authors to respond to: Do these culture cells behave in a similar fashion to *in vivo* responses? I know you alluded to the fact that they did; however, do you have other pieces of information that suggest that these cells do respond as the *in vivo* responses have demonstrated before?

Two, are there receptors for endotoxin on these cells, and has that been characterized in this cell line? And I'm not educated about this particular cell line. This is a very complex inter-relationship, as has been implied. I am curious about the mechanism by which the dexamethasone participates in this diminished response, as you have demonstrated.

Three, do you have any data on the effects of platelet-activating factor in such a system in this model, or have you used any specific antagonists or monoclonal antibodies to sort out the specific effects? The mechanisms involved in cellular effects in sepsis are very important, and I applaud the authors for their contributions in this field and with their elegant studies. In general, *in vitro* studies are important in defining mechanisms, as Dr. Copeland implied, as did Dr. Fischer. I would caution against an interpretation that implies that these data are applicable directly to the *in vivo* systems. I want to thank the Association for the privilege of discussing this paper.

DR. EDWARD M. COPELAND III (Closing discussion): To take Drs. Fletcher and Fischer's questions together: Correct, you cannot take experiments done *in vitro* and apply them directly to an *in vivo* model. On the flip side of that coin, I think probably in the field of surgery, we have been able to make such applications better than virtually any other medical field. So I just offer that observation. Dr. Wiley Souba and a couple of the physiologists at our place have been the people who described various sodium-dependent and sodium-independent transport mechanisms. In fact, Dr. Souba and Dr. Bruce Stevens described what they call System B. So we are in a new frontier here, and many of the things that both Drs. Fletcher and Fischer suggest are experiments that need to be done. We appreciate their suggestions, are glad that they are recorded, and are in fact doing some of the experiments currently. For example, to move on to Dr. Garrison's questions, hypoxia clearly has an effect; pH clearly has an effect. The pH of the jejunal brush border is probably neutral simply because of pancreatic juice and bile and because of the mucous layer covering it. Nevertheless, pH does need to be studied. I am absolutely certain that hypoxia, particularly in an endotoxic shock model, will have an effect. Nitric oxide, a very popular compound for all of us studying metabolism today, probably has an effect. Endotoxin, no doubt, poisons the sodium potassium ATPase transporter. What this effect will be is unclear.

We are investigating hypoxia now. You can plate CACO-2 cells on Millipore filters to study a hypoxic effect. By such a mechanism, you can study both the luminal side and the basal lateral membrane side. We hope to have some of this information available for you soon. As an enterocyte matures to the top of a villous, it becomes a cell that participates in absorption, nitrogen processing, and reprioritization of glutamine delivery. Glutamine, of course, is an important fuel for virtually all organs. The major process of glutamine and its major utilizer is the gastrointestinal tract, particularly the small bowel. But other organs need glutamine, and there is a limited supply of it during critical illness. The fact that the gut downregulates its need for glutamine when the liver, fibroblasts, and immunologically active cells have an increased need for glutamine is quite interesting and may be the reason that endotoxin or sepsis downregulates the gut's need for glutamine. The gut cannot tolerate this downregulation very long, obviously, but we do not know how long "long" is. Returning to Dr. Fletcher's questions about what happens to CACO-2 cells if you leave them exposed to cytokines for lengthy periods of time, I do not honestly know the answer. Prolonged exposure, however, to an acid pH, hypoxia, or certain cytokines may result in bacterial translocation.

Dr. Garrison asks how cytokines gain access to the lumen? Well, lymphocytes are within the bowel wall and produce cytokines. Bacteria die and release endotoxins. So, I think there are multiple ways cytokines gain access to the lumen. Cytokines clearly gain access to the basal lateral membrane via the circulation or via local production in Peyer's patches. Have we used antagonists? No. Dexamethasone functions as a stress hormone and, in this particular experiment, its effect was permissive and potentiated the decrease in glutamine transport when combined with interleukin-1 and tumor necrosis factor.

Patterns of Ileal Recurrence in Crohn's Disease

A Prospective Randomized Study

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To gain information on the pathogenesis of ileal recurrence, 86 patients with Crohn's disease undergoing their first ileocolic resection were randomized to receive either an end-to-end (n = 47) or side-to-end (n = 39) anastomosis. The demographic and clinical characteristics of both groups were similar. There were no statistically significant differences between the two groups in postoperative complications or in the subsequent development of symptomatic or documented recurrences. Among the 43 patients with follow-up in the end-to-end anastomosis group, there were 10 documented ileal recurrences (23%), and all involved distal ileum in the characteristic preanastomotic location. Among the 35 patients with follow-up in the side-to-end anastomosis group, there were 11 documented recurrences (31%, not significant). The ileal recurrence pattern could be determined accurately in five of these 11 patients and involved the ileum adjacent to the colon, but spared the distal ileum in the blind pouch. This study suggests that the fecal stream and reflux of colonic contents are important factors in determining the pattern of ileal recurrence after ileocolectomy for Crohn's disease.

RECURRENCE OF CROHN'S disease after resection of distal small bowel and proximal colon characteristically involves the small bowel just proximal to the anastomosis.[1,2] This typical recurrence pattern was noted by Crohn in his original article published in 1932.[3] He attributed preanastomotic recurrence to inadequate resection, assuming that residual disease had been left in the distal ileum. A variety of other explanations have been offered for the pattern of recurrence after resection.[4] These include passage of an agent from mesenteric lymph nodes to the resection margin; the presence of the suture line itself, which could induce local ischemia or local immunologic changes; or reflux of colonic contents into the ileum.[2,4] Restoration of enteric continuity by side-to-end anastomosis allows assessment of some of these explanations. With this type of anastomosis, a small blind pouch of ileum is exposed to mesenteric lymph nodes and contains a suture line, but is not directly in the fecal stream and should not be exposed to reflux of colonic contents. Therefore, a prospective randomized study was carried out to compare similarities and differences in the recurrence pattern after end-to-end and side-to-end anastomosis (Fig. 1).

Clinical Material

Between April of 1983 and February of 1991, 92 patients undergoing first-time resection of terminal ileum and proximal right colon for Crohn's disease were randomized to receive either an end-to-end or side-to-end anastomosis. Randomization was performed at the beginning of the operative procedure by picking from an envelope a card on which was written either end-to-end or side-to-end. Six patients were subsequently excluded from analysis. In two patients the pathology of the resected specimen did not confirm the preoperative diagnosis of Crohn's disease. In one patient, an end-to-side anastomosis was performed in error instead of a side-to-end ileocolostomy. An additional patient underwent a side-to-side anastomosis for technical reasons. A decision was made in a fifth patient, after randomization, not to perform a resection. The final patient had only small bowel resected, and therefore was excluded. This left 86 patients in the study.

All patients underwent resection of all gross disease in the terminal ileum, or terminal ileum and proximal colon,

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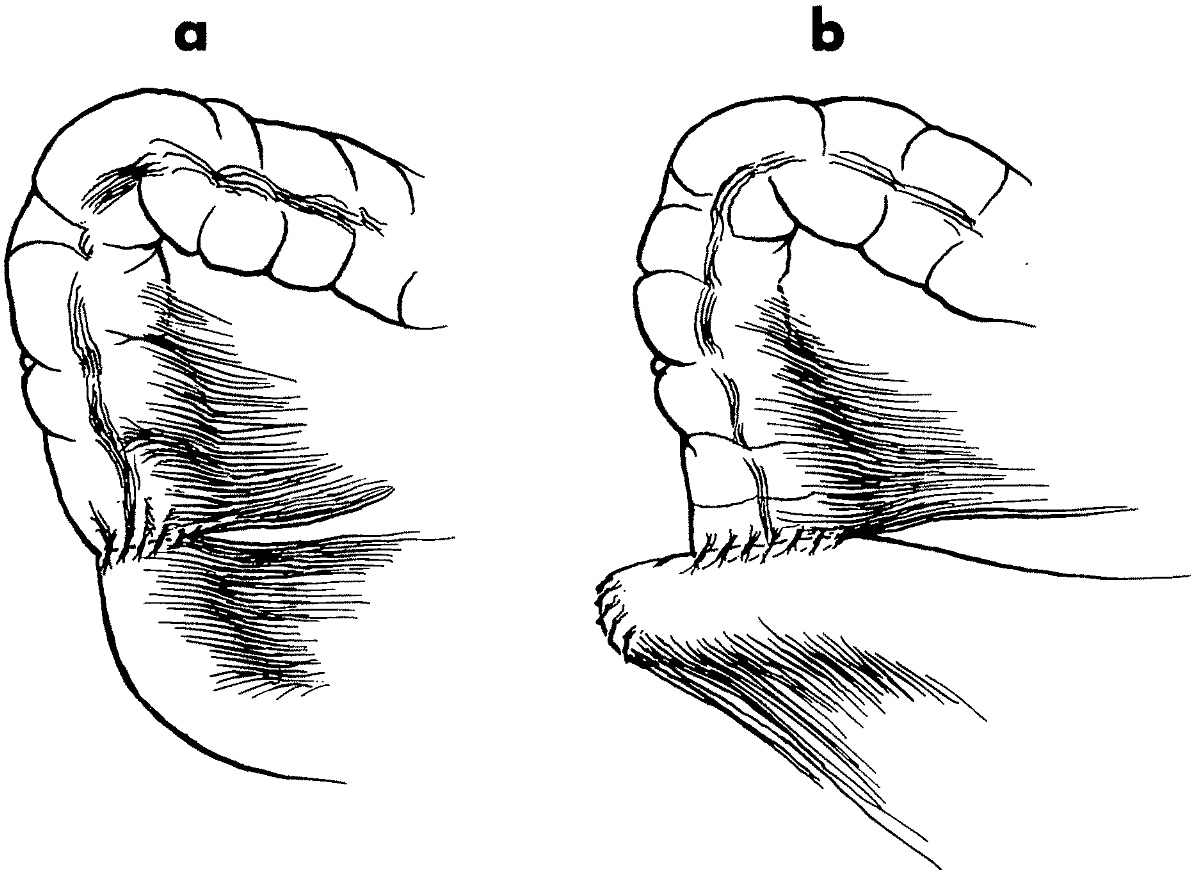

FIG. 1. After ileocolic resection, the ileocolostomy was performed in either (A) an end-to-end or (B) a side-to-end fashion on a random basis.

taking approximately a 5-cm margin of normal bowel both proximally and distally. End-to-end anastomoses were performed in a standard fashion with an inner continuous layer of absorbable synthetic suture material, and an outer layer of interrupted silk. Side-to-end ileocolostomies were performed with a similar technique, after closing the end of the ileum with an inner continuous layer of absorbable synthetic suture material, and an outer layer of interrupted silk. The blind pouch of ileum in the side-to-end group was approximately 1 inch in length.

Age of the 86 patients ranged from 12 to 68 years, with a mean of 31 years. Thirty-nine patients were men, and 47 were women. Disease duration before surgery ranged from 0.2 to 25 years, with a mean duration of 6.4 years. Body weight ranged from 34 to 99 kg, with a mean weight of 60 kg. Preoperative hematocrit varied from 28% to 49%, with a mean of 37%. White blood count ranged from 3.1 to 21 thousand, with a mean of 9.8 thousand. Serum albumin levels ranged from 2.3 to 5 g/dL, with a mean of 3.9 g/dL (Table 1).

The most common indications for surgical intervention were partial intestinal obstruction with crampy abdominal pain and diarrhea, fistula formation, or intra-abdominal abscess (Table 2). Before surgery, all patients had received drugs in an attempt to ameliorate their symptoms, and to control their inflammatory bowel disease. The medications used and the length of time administered were extremely variable. At surgery, all patients underwent resection of the terminal ileum and proximal colon for ileal or ileocolic Crohn's disease. In addition, eight patients had resection of another segment of small bowel (1) or large bowel (7), one had a stricturoplasty performed, 31 had division of one or more entero-enteric, enterovesical,

TABLE 1. *Patient Demographics*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Age (yr)	31 (12–60)	31 (14–68)	31 (12–68)
M/F	19/28	20/19	39/47
Disease duration (yr)	6.3 (0.2–20)	6.6 (0.5–25)	6.4 (0.2–25)
Weight (kg)	60 (34–94)	61 (34–99)	60 (34–99)
Hematocrit (%)	37 (28–43)	38 (30–49)	37 (28–49)
White blood count (1000)	9.7 (3.1–21)	9.9 (5.0–16.1)	9.8 (3.1–21.0)
Albumin (g/dL)	3.8 (2.3–5.1)	4.0 (2.9–5.0)	3.9 (2.3–5.1)

TABLE 2. *Indications for Surgery*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Surgical indications			
Total obstruction	0	1	1
Partial obstruction	41	33	74
Bleeding	0	1	1
Perforation	1	0	1
Fistula	16	15	31
Abscess	6	4	10

Some patients had more than one indication for surgery.

TABLE 3. *Operative Management and Postoperative Course*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Length of resection			
Small bowel (cm)	28 (1–90)	29 (6–120)	28 (1–120)
Large bowel (cm)	9 (1–39)	10 (3–40)	9 (1–40)
Pathology			
Active	44	39	83
Inactive	3	0	3
Other operative procedures			
Small bowel resection	1	0	1
Large bowel resection	2	5	7
Strictureplasty	1	0	1
Division of enterofistula into			
Bowel	9	10	19
Bladder	5	8	13
Vagina	2	1	3
Drainage of intra-abdominal abscess	6	4	10
Postoperative complications			
Urinary tract infection	1	0	1
Small bowel obstruction	0	2	2
Wound infection	0	1	1
Fever	0	1	1
Total	1	4	5
Postoperative mortality rate	0	0	0
Postoperative days	8 (5–12)	9 (6–16)	8 (5–16)

or enterovaginal fistulas, and 10 had drainage of an intra-abdominal abscess.

Forty-seven patients were randomized to receive an end-to-end ileocolostomy, and 39 patients were randomized to receive a side-to-end ileocolostomy. The demographics and clinical characteristics of these two groups did not differ significantly one from the other, or from the group as a whole (Table 1). A mean of 28 cm of small bowel and 9 cm of large bowel were resected in those patients undergoing an end-to-end anastomosis, as compared with a mean of 29 cm of small bowel and 10 cm of large bowel in those undergoing a side-to-end anastomosis. A total of 26 other operative procedures were performed at the same time in those patients undergoing an end-to-end anastomosis, as compared with 24 other procedures performed in the group undergoing a side-to-end anastomosis. These differences were not statistically significant (Table 3). The pathology specimens demonstrated active disease in 44 of the 47 patients undergoing resection and end-to-end anastomosis, as compared with all 39 patients in the side-to-end anastomosis group.

There were no hospital deaths. After surgery there was one postoperative complication in the end-to-end group, and mean postoperative hospital stay was 8 days. In the side-to-end group, there were four postoperative complications, with a mean stay of 9 days. These differences were not statistically significant (Table 3). In addition, one patient in the side-to-end group developed symptoms 5 months after surgery, and a barium study demonstrated a small fistula leading from the end of the blind pouch. The patient was explored, the anastomosis resected, and an end-to-end ileocolostomy performed. Histopathologically there was no evidence of Crohn's disease in the specimen.

Clinical Course

Patients followed at The Johns Hopkins Hospital were seen periodically during the course of the study. These patients, and patients not followed at The Johns Hopkins Hospital, were contacted annually by questionnaire. Each patient's physician also was contacted annually. Follow-up information was available for 78 of the 86 patients. Follow-up ranged from 5 to 94 months, with a mean of 47 months. There was no statistical difference in length of follow-up in the end-to-end and side-to-end groups (Table 4).

A symptomatic recurrence was defined as abdominal pain or diarrhea that occurred at least once a week during follow-up. Forty of the 78 patients (51%) developed symptomatic recurrences. The prevalence was identical for both anastomotic groups (Table 4). Recurrence at the ileocolic anastomosis was documented in 10 of the 43 patients undergoing end-to-end anastomosis (23%), and

TABLE 4. *Clinical Course*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Patients with follow-up	43	35	78
Duration (mo)	49 (6–94)	45 (5–91)	47 (5–94)
Symptomatic recurrence	22 (51%)	18 (51%)	40 (51%)
Documented recurrence at anastomosis	10 (23%)	11 (31%)	21 (27%)

TABLE 5. *Ileal Recurrences*

	Type of Anastomosis		
	End to End	Side to End	Total
Documented	10	11	21
Documented by			
Surgery	3	6	9
Barium studies	5	3	8
Endoscopy	2	2	4

in 11 of the 35 patients undergoing side-to-end anastomosis (31%). This difference was not statistically significant. In the end-to-end group, the recurrences were documented by surgery (n = 3), barium studies (n = 5), and endoscopy (n = 2). In all 10 patients developing a recurrence in the end-to-end group, the recurrence involved the distal ileum just proximal to the anastomosis. In the side-to-end group, the recurrences were documented by surgery (n = 6), barium studies (n = 3), and endoscopy (n = 2) (Table 5). In 5 of the 11 patients with a recurrence at the anastomosis in the side-to-end group, the anatomy of the recurrence could be accurately determined. Four of these patients were operated on, and one underwent colonoscopy. In each of the five patients whose recurrence could be documented, the recurrence was in the ileum adjacent to the colon at the anastomosis. Of particular note, the 1 inch of distal blind ileum in the side-to-end anastomosis was grossly normal (Fig. 2). In two of the patients in the side-to-end group requiring resection, the surgery was performed elsewhere and the exact pattern of recurrence could not be determined. In addition, in three patients in whom the recurrence was documented radiographically, and in one determined by endoscopy, the recurrence pattern at the anastomosis could not be determined accurately.

As was the case before operation, most patients received a wide variety of medications after operation to control or prevent symptoms or recurrence of their inflammatory bowel disease. These medications were administered for variable lengths of time. There were no discernible patterns in either group.

Discussion

The preanastomotic recurrence pattern after resection has fascinated physicians since Crohn's initial report,[3] but very little information explaining this phenomenon has evolved. The current study was carried out primarily to gain information as to factors that might influence this characteristic recurrence pattern. In addition, little information is available concerning the influence of the type of anastomosis on the subsequent course of Crohn's disease. Over the years, surgeons have treated Crohn's disease by surgical bypass, surgical exclusion, and surgical resection with end-to-end, side-to-end, end-to-side, or side-to-side anastomosis. There are virtually no controlled studies to support one anastomotic procedure over another. This study therefore also served as a basis to compare two different types of surgical anastomoses after resection for Crohn's disease.

The randomization process resulted in two groups of patients that were similar demographically. For age, sex, body weight, and disease duration, there were no statistically significant differences between the two groups. In addition, when hematocrit, white blood count, and serum albumin are used as criteria, both groups were healthy and comparable. In terms of indications for surgery, the amount of bowel resected at surgery, and the number of patients with active disease, both groups were also comparable. Thus the only clear difference between the two groups was the means by which enteric continuity was re-established after resection of the terminal ileum and proximal colon. In one group, an end-to-end anastomosis was performed. This is perhaps the anastomosis that is now most commonly used after resection of terminal ileum and proximal colon in patients with Crohn's disease. The second group received a side-to-end ileocolostomy. Although end-to-side and side-to-side anastomoses are more commonly used, a side-to-end anastomosis was chosen for the second group so that a segment of distal ileum extended beyond the anastomosis to test the possible explanations of preanastomotic recurrence.

Both groups of patients had similar courses after surgery. Length of follow-up was similar for both groups, an identical number of symptomatic recurrences developed in each group, and there was no statistically significant difference between the groups in the incidence of documented recurrence at the anastomosis. Thus, there was no clear advantage of one type of anastomosis over the other, and the clinical course of both groups was comparable. However, one patient in the side-to-end group developed a small fistula from the blind pouch 5 months after surgery and required re-exploration. Because there was no evidence of Crohn's disease in the specimen, this complication could be attributed to the side-to-end anastomosis.

The main purpose of the study was to compare the pattern of recurrence in each of these two types of anastomosis. As was expected, the recurrence pattern in those patients who had undergone an end-to-end anastomosis assumed the characteristic pattern of disease in the preanastomotic distal ileum, generally stopping at the suture line. By contrast, the five patients in the side-to-end anastomosis group in whom the anatomy of the recurrence could be adequately determined showed sparing of the distal portion of the ileum contained in the blind pouch. Rather, the recurrent disease developed in the ileum immediately adjacent to the ileocolostomy.

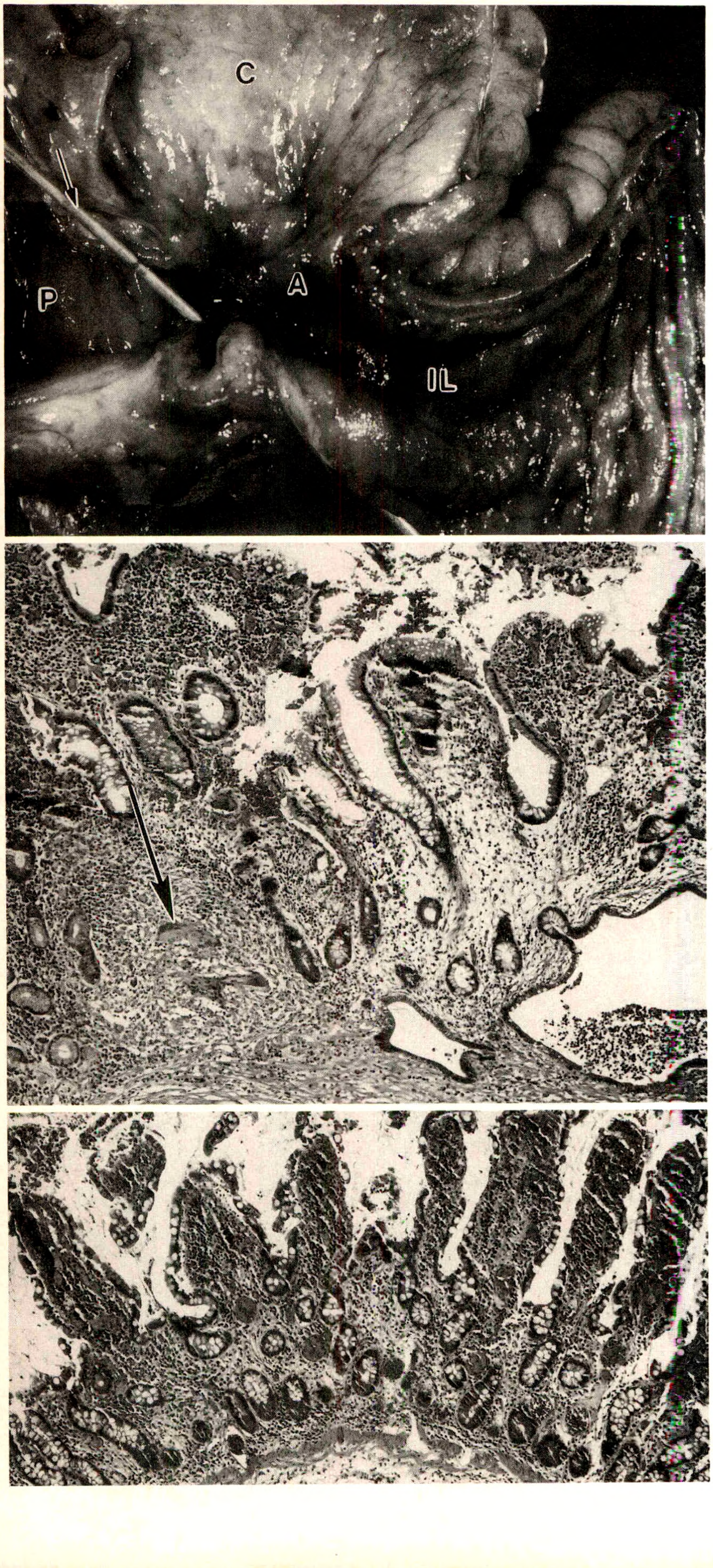

FIG. 2. Resected specimen of side-to-end ileocolonic anastomotic site with recurrent Crohn's disease. (A, top) In the gross specimen, the recurrence involves the ileum (IL) at the anastomotic site (A) with the colon (C). At this site, the ileum is strictured and gives rise to a fistula tract (containing probe indicated by arrow). By contrast, the blind pouch (P) of ileum distal to the anastomotic site is spared by recurrent Crohn's disease (×1.1). (B, center) Histopathologic features of preanastomotic ileum. Active Crohn's disease is manifested by a crypt abscess, noncaseating epithelioid cell granuloma (arrow) with pyloric metaplasia of adjoining ileal glands, villous blunting, chronic inflammation of the lamina propria, and fibromuscular proliferation of the subjacent muscularis mucosae (H&E, ×70). (C, bottom) Histopathologic features of blind ileal pouch distal to anastomotic site. Only mild villous blunting and chronic inflammation of the lamina propria are present, and there is no evidence of active Crohn's disease (H&E, ×70).

Even though the recurrence pattern seen in Crohn's disease has been recognized since Crohn's initial report, a logical explanation of this characteristic pattern has not been forthcoming. Initially, as Crohn suggested,[3] it was thought that inadequate resection left residual disease in the distal ileum. Because microscopic disease is often present throughout the entire small and large bowel,[5] and is no more likely at the resection margin than elsewhere, this explanation now seems untenable. Others have suggested that if the surgeon leaves hypertrophied lymph nodes behind in the root of the small bowel mesentery, some residual agent subsequently passes up to the ileal margin and is responsible for the recurrence. Although this theory has received support for many years, surgeons have been reluctant to perform the radical resections that would be required if one were to try to remove all of the enlarged lymph nodes in the root of the mesentery. The current study would appear to eliminate both of these explanations as possibilities. First, the recurrence pattern in patients who underwent a side-to-end anastomosis did not involve the distalmost portion of the ileum. If leaving residual disease behind at the resection margin, or leaving hypertrophied lymph nodes behind that contained an agent that would pass up to the resection margin of the distal ileum were important, the recurrence would have involved the distal ileum in the blind pouch. That was not the case, and in fact the blind pouch was spared grossly in all five instances in which the recurrence pattern could be determined. Furthermore, the pouch was spared histopathologically in all but one of the specimens resected at Hopkins. Finally, the suture line itself did not appear to be an important factor in determining recurrence because there was a suture line in the end of the blind pouch.

The recurrence pattern that was seen in the patients who developed recurrence after a side-to-end anastomosis suggests that the fecal stream and reflux of colonic contents into the ileum are important factors. Supporting evidence for this includes a unique patient recently seen at Hopkins who underwent resection of the terminal ileum for Crohn's disease. In the middle of the diseased bowel there was a narrow mouthed diverticulum, presumably relatively isolated from the fecal stream. The diverticulum was spared by the inflammatory process, and its mucosa was histopathologically uninflamed. In addition, Rutgeerts et al[6] have recently reported five patients who underwent ileocolectomy for Crohn's disease. All five patients underwent an ileocolostomy anastomosis, but were diverted proximally by an ileostomy. Six months later, endoscopy with biopsy showed no gross or microscopic disease in the neoterminal ileum. The ileostomies were then taken down and the fecal stream re-established over the neoterminal ileum. Six months after ileostomy takedown, endoscopy and biopsy demonstrated gross and microscopic Crohn's disease in the neoterminal ileum in all five patients. This study provides additional strong support for our evidence that the fecal stream and reflux of colonic contents into the ileum are important factors in determining the site of recurrence in Crohn's disease. This characteristic recurrence pattern in Crohn's disease undoubtedly contains important clues to the pathogenesis of this disease.

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DISCUSSION

DR. GEORGE BLOCK (Chicago, Illinois): President Ochsner, Dr. Jones, Fellows of the Association, I wish to express my pleasure and my appreciation for your generosity and forbearance in electing me to membership in this distinguished group. I look forward to participation for many years and not only thank you but specifically thank my sponsors, Dr. Harrington, Dr. Sawyers, and Dr. Cohn.

Dr. Cameron's presentations are always provocative, sometimes perplexing. Today's are both provocative and perplexing. They are provocative because Dr. Cameron espouses the conventional wisdom. This is an unusual role for Dr. Cameron; he usually challenges conventional wisdom such as the anastomotic recurrence. It is perplexing because it is at variance with some of our own observations. Obviously, we use different methods of achieving our conclusions. His was a prospective study; ours was retrospective. He has relied on operative specimens, endoscopy, and radiographs; we believed and do believe that radiographic and endoscopic determinations of the exact pattern of recurrence are not reliable and look only to the examination of the resected specimens. We looked at several hundred of our patients who had recurrences. And they followed conventional wisdom for a segment of population. Fewer than one third had preanastomotic recurrences in the ileocolic group of Crohn's disease. Some of them or a good number of them were postanastomotic, and many of them were far distant from the anastomosis. This is not explainable by the thesis that Dr. Cameron has elaborated today, that the recurrence of Crohn's disease in the ileal segment is due to colonic reflux; I would caution against making this conclusion on the basis of five patients. This is almost anecdotal evidence. But if this thesis is correct, then we should perhaps vary our approach to this disease by trying to design some operation that would prevent colonic reflux, such as no anastomosis at all, and a stoma in all patients. Yet we know that patients who do have stomas and, for one reason or another, do not have anastomosis at the primary operation, are heir to recurrence usually below the fascial line of the stoma. We could, perhaps, do a total colectomy and abrogate the colon completely. Dr. Cameron's observations give some credence to the observation that in those patients in whom we mistakenly do a total colectomy and endorectal pull-through for what we find to be Crohn's disease, it is not the disaster that we have been led to believe. There are recurrences, but they are not the immediate and devastating recurrences. Perhaps we should do some type of a nipple valve operation, not unlike a Kock pouch, to prevent reflux. Or we should alter the colonic content. Now how do we alter the colonic content? Do we alter the flora? Do we alter the bile acids? Do we alter the amines? I do not have the vaguest idea what we would alter in these patients and would ask Dr. Townsend to help us in that. So my question to Dr. Cameron is, if this thesis is accepted and is valid, is the next portion of your work to make some clinical approach to eliminating or decreasing the colonic reflux so as to delay or perhaps totally abrogate the appearance of the preanastomotic reappearance of Crohn's disease? I enjoyed the paper greatly and appreciate Dr. Cameron's providing me with the manuscript to read last night, and I thank you all for the privilege of the floor and, again, for the privilege of membership.

DR. BRUCE WOLFF (Rochester, Minnesota): Thank you, Dr. Ochsner. I still consider myself a Georgian since I was born and brought up there, although I have been translocated.

Dr. Jones, Members of the Association, I find this a very interesting paper, and I enjoyed very much being able to hear it. I, like Dr. Block, wonder about a third group of patients, those patients in whom an ileostomy might have been done on a temporary basis perhaps for a year or 2, and the recurrence rate in that group. In our experience, the recurrence rate in that particular group with an ileostomy has been lower than in the groups that have had anastomosis. And if that were the case, that would certainly lend credence to the theory of something in reflux of colonic contents contributing to or causing the recurrence. There is a study in Sweden presently showing this to be the case, and I would be very interested to know if the authors plan a prospective, randomized study. I know that is a very difficult thing to do, when a patient would be offered an ileostomy as opposed to an anastomosis, but I think that would be an important study and might lend credence to the theory of something in the fecal stream that would contribute to the recurrence rate.

I want to congratulate the authors on being able to do a prospective randomized study in Crohn's disease. It is a very difficult thing to do, and I think they have done a wonderful job, and it has taken some years to do it. Thank you.

DR. J. L. CAMERON (Closing discussion): I would like to thank both Dr. Block and Dr. Wolff for their comments. I think our studies present a substantial argument that the fecal stream and reflux of colonic contents are important in the ileo-recurrence pattern seen in Crohn's disease. We have another ongoing prospective study in which we operate on patients who have been operated on previously, and are undergoing second, third, and fourth ileocolic resections. And in that second study of patients undergoing reoperation, if they have had their initial anastomosis in an end-to-end fashion — and most have — we are putting them back together in a side-to-end fashion. So each patient is serving as his or her own control. In that study, as in the current study, the recurrence is adjacent to the colonic anastomosis, and by and large the ileal pouch is spared or is nearly spared. Sometimes the histology is absolutely normal; other times there is some histologic change, but the basic pattern is virtually identical.

There is another study that was recently reported that confirms ours, and it comes from the Netherlands. After doing an ileocolic resection and anastomosis, the group from the Netherlands did an ileostomy proximally. They then did colonoscopies on the patients at 6 months, and there was no evidence of disease in the neoterminal ilium or in the colon at the anastomosis. They then took down the ileostomy 6 months later, recolonoscoped the patients, and there were recurrences in the preanastomotic ileum, suggesting, as did our study, that exposure to the fecal stream and reflux of colonic contents are important. These studies certainly do not explain all ileal or colonic recurrences in Crohn's disease, but I think they do explain the characteristic pattern that is seen most commonly.

Now, how can we use this information to modify, decrease, or eliminate recurrences? That step is obviously more difficult. We have been reluctant to consider creating a valve to prevent reflux from the colon to the ileum. I think we are leaning at this point toward trying to modify the colonic bacterial flora in some way. Many physicians and gastroenterologists are convinced that a variety of antibiotic regimens will decrease recurrences in Crohn's disease. Perhaps by modifying the bacterial flora in the colon, the incidence or prevalence or timing of a recurrence could be decreased. Thank you.

Prostaglandin E_2 Production During Hepatic Regeneration Downregulates Kupffer Cell IL-6 Production

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The liver possesses the remarkable ability to regenerate to its original size after a 70% partial hepatectomy. There has been little effort to characterize the Kupffer cells' role in this unique mammalian reparative physiologic phenomenon. The capacity of rat Kupffer cells (KC) isolated at specific intervals after partial hepatectomy to produce interleukin-6 (IL-6) and prostaglandin E_2 (PGE_2) in response to endotoxin was evaluated in standard RPMI-1640 (1200 μM L-arginine) and arginine-depleted RPMI-1640 (10 μM L-arginine) media. Regenerating liver KC 48 to 120 hours after partial hepatectomy responded to endotoxin stimulation with a significantly greater ($p < 0.05$) production of IL-6 in standard RPMI-1640. Because Kupffer cells function in an environment where high arginase activity results in negligible L-arginine levels, the 10 μM L-arginine RPMI-1640 was used to simulate the true hepatic microenvironment. Production of IL-6 by regenerating liver KC was further increased ($p < 0.05$) by placing these same KC in 10 μM L-arginine RPMI-1640 tissue culture media. During the same period, regenerating liver KC produced significantly ($p < 0.01$) more PGE_2 than sham-operated KC in both standard and low-arginine media. When the cyclo-oxygenase inhibitor indomethacin (1×10^{-5} M) was added to cultures, the PGE_2 production was inhibited, and IL-6 production was upregulated ($p < 0.05$) in arginine-depleted cultures. The authors conclude that during hepatic regeneration KC IL-6 production is elevated but controlled in an autoregulatory fashion by KC PGE_2 production.

MAMMALIAN LIVER POSSESSES a remarkable regenerative capacity after surgical partial hepatectomy or hepatic injury.[1] Recognition of this unique mammalian process has led to extensive research attempting to identify substances that initiate and terminate hepatic regeneration.[2,3] These investigative efforts have identified several humoral factors,[4-6] portal blood factors,[2,7] and liver-derived growth factors[3,3] that stimulate liver regeneration in *in vivo* experimental models, but little effort has been made to characterize the alterations that occur in the liver's resident macrophage, the Kupffer cell (KC), during this unique phenomenon. Several investigators have suggested that the reticuloendothelial system plays an important role in regeneration of the rat liver because reticuloendothelial system blockade depressed hepatocellular proliferation after partial hepatectomy.[9,10]

Kupffer cells constitute over 90% of the host reticuloendothelial system,[11] and are juxtaposed anatomically with the hepatocytes, which are the predominant regenerating parenchymal mass.[12] West et al.[13,14] reported that the stimulated Kupffer cell may inhibit the types and quantities of individual proteins being synthesized by hepatocytes, and may play a role in the development of hepatic failure during sepsis, endotoxemia, or after extended liver resection. Therefore, prevention of the negative impact of the KC on hepatocyte function may promote hepatic regeneration and improve the survival of the host during these periods of physiologic stress. Kupffer cells produce the cytokine interleukin-6 (IL-6), which is known to affect the hepatocytes' acute phase response to injury[15] and plays a role in hepatocyte proliferation.[16] Prior studies on hepatic regeneration and KC–hepatocyte interactions have not determined the influence of this cytokine nor the L-arginine concentration of the tissue culture medium being used. Callery et al.[17] have recently reported that the production of prostaglandin E_2 (PGE_2)

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by the KC during the initial stage of hepatic regeneration was elevated and that the KC production of tumor necrosis factor-α was markedly decreased.[18] Because KC production of cytokines and eicosanoids may affect the systemic immune response, as well as the hepatocyte responses, we compared the capacity of KCs with other macrophage populations to produce IL-6 and determined whether this production was regulated by PGE_2 in both standard RPMI-1640 (1200 μM L-arginine) and low arginine (10 μM L-arginine) RPMI-1640 tissue culture media during hepatic regeneration after a 70% partial hepatectomy in the rat.

Materials and Methods

Animals

Male Sprague-Dawley rats weighing 225 to 250 g were used at 10 to 12 weeks of age, and were cared for according to specific National Institutes of Health guidelines. Animals were provided a nutritionally balanced rodent diet (5001, Purina Mills, St. Louis, MO) and water *ad libitum* and were not fasted before use.

Operative Procedures

Under ether anesthesia, 70% partial hepatectomies (PHx) were performed through a 3.0-cm. midline incision by resecting the median and left lobes of the rat liver, as outlined by Higgins and Anderson.[1] Sham operations consisted of a midline laparotomy with gentle manipulation and exteriorization of the median and left liver lobes. All operations were performed between 8:00 and 10:00 A.M. to avoid the effects of diurnal variations on the regenerative response.[19]

Kupffer Cell Isolation and Purification

Kupffer cells were harvested from animals for *in vitro* analysis at 48, 120, 168, and 336 hours after partial hepatectomy or sham operations. While under anesthesia, the animal was exsanguinated and the liver was perfused *in situ* through the portal vein with Hank's balanced salt solution (HBSS). The livers were dissected free and passed through 60-μm brass screens into HBSS containing 1% HEPES buffer and 1% penicillin/streptomycin. After centrifugation at 500*g* for 10 minutes (4 C), the pellet was resuspended in 30 mL antibiotic-supplemented HBSS containing 0.01% collagenase (type I, 240 U/mg, Worthington Biochemicals, Freehold, NJ), 0.001% deoxyribonuclease (type 1, 60 U/mg, Sigma Chemicals, St. Louis, MO), and 1 mM $CaCl_2$, and incubated for 45 minutes in a 37 C agitating water bath. After centrifugation at 50*g* for 2 minutes to sediment hepatocytes, an enriched nonparenchymal cell pellet was obtained by centrifugation of the supernatant at 500*g* for 10 minutes. Erythrocytes were lysed by incubation for 3 to 5 minutes with ammonium chloride (0.83%). The cells were washed twice with HBSS, and resuspended in either standard RPMI-1640 (1200 μM L-arginine) or low-arginine (10 μM) RPMI-1640 tissue culture media without arginine containing antibiotics and 10% fetal calf serum (low-endotoxin, heat-inactivated, Gibco, Grand Island, NY). After 4 hours of incubation at 37 C in 100-mm plastic petri dishes (Costar, Cambridge, MA), nonadherent cells were removed by three successive washes with warm HBSS. Adherent cells, phagocytosing 0.8 μm latex beads (Sigma), are designated as KCs. After 10 minutes' incubation at 37 C in Trypsin-ethylenediaminetetra-acetic acid (0.05%/0.02%), KC were liberated from the plastic dishes by vigorous pipetting, and washed and counted. Kupffer cell purity was >95% by latex bead ingestion, and viability was > 90%, as indicated by trypan blue exclusion (0.4% trypan blue stain in 0.85% saline, Gibco Laboratories).

Splenic, Peritoneal, and Alveolar Macrophage Isolation

Resident splenic, peritoneal, and alveolar macrophages were isolated from the same rats providing KC. Peritoneal macrophages were isolated before the harvest of liver by repeatedly lavaging the intact abdominal cavity with 37 C HBSS. Alveolar macrophages were recovered after KC harvest by directly cannulating the trachea and repeatedly lavaging the tracheobronchial tree with 37 C HBSS. Splenic macrophages were harvested by passage of the spleen through a 60-μm brass screen, differential centrifugation and plastic adherence, as described for the KC isolation technique. Ninety-five per cent of the splenic, alveolar, and peritoneal macrophages excluded trypan blue and phagocytized latex beads.

Culture Media

Kupffer cells (5×10^5) were suspended in one of two different preparations of culture media of RPMI-1640 (Gibco Laboratories, Grand Island, NY) containing 1% HEPES buffer, 1% nonessential amino acids, 1% L-glutamine, 1% penicillin/streptomycin, and 10% fetal calf serum (low endotoxin, Hyclone Labs Inc., Logan, UT). Arginine concentration in the culture media was the only variable in these experiments. Standard RPMI-1640 (+Arg) contained 1200 μM L-arginine, whereas arginine-depleted RPMI-1640 (−Arg) contained only approximately 10 μM L-arginine (verified by high-performance liquid chromatography performed by the Gibco Corp., Grand Island, NY), which was derived from the addition of 10% fetal calf serum.

Culture Protocol

After purification, 5×10^5 sham or PHx KC, splenic macrophages, peritoneal macrophages, and alveolar macrophages in 1 mL complete KC media were plated in 24-well culture dishes (Costar). After overnight culture, KC were repleted with fresh media and stimulated with 2.5 μg/mL bacterial lipopolysaccharide (LPS, *Escherichia coli* type 0111:B4, Difco Laboratories, Detroit, MI). Supernatants were collected at timed intervals, sterile filtered (0.2-μm Acrodisc, Gelman Sciences, Ann Arbor, MI), and stored at −80 C until use.

Prostaglandin E_2 Radioimmunoassay

Partial hepatectomy and sham KC supernatants were assayed for PGE_2 by competitive binding radioimmunoassay. Samples were combined with ^{3}H-labeled PGE_2 (New England Nuclear, Boston, MA) and a specific rabbit antisera to PGE_2 (provided by Dr. Aubrey Morrison, Department of Pharmacology, Washington University). After a minimum 12-hour incubation at 4 C, the excess ^{3}H-PGE_2 was removed with a charcoal–dextran mixture and the bound portion counted by liquid scintillation spectroscopy. Triplicate values were averaged and compared with a standard curve performed with each assay. The lack of cross-reactivity of the antisera with competing eicosanoids has been previously verified.[20]

Interleukin-6 Bioassay

Partial hepatectomy and sham KC supernatants were collected at timed intervals and IL-6 activity measured by proliferation of the IL-6–responsive B9.9 cell line (provided by Dr. Lucian Aarden, Netherlands, through Dr. Richard Nordan, National Institutes of Health). Serially diluted supernatant samples were incubated at 37 C in 5% CO_2 for 44 hours with 2×10^3 B9.9 cells. ^{3}H-thymidine (2 μCi/well) was added for the final 4 hours of culture. The cultures were harvested at 48 hours after culture initiation by using an automatic cell harvester onto glass fiber filters. Radioactivity was determined by liquid scintillation spectrometry using an LKB (1272 Clinigamma, LKB, Turku, Finland) liquid scintillation counter. Unknown supernatant IL-6 levels were determined by comparison with a standard curve of B9.9 proliferation to known quantities of recombinant human IL-6 (Genzyme, Boston, MA).

Statistical Analysis

Data are representative of three independent experiments, each performed in triplicate, and analyzed for significance by analysis of variance.

Results

Effects of 70% Partial Hepatectomy on KC IL-6 Production

Hepatic regeneration is greatest 48 to 120 hours after 70% PHx. Regenerating KC demonstrated a significantly ($p < 0.05$) greater capacity to produce IL-6 at all culture

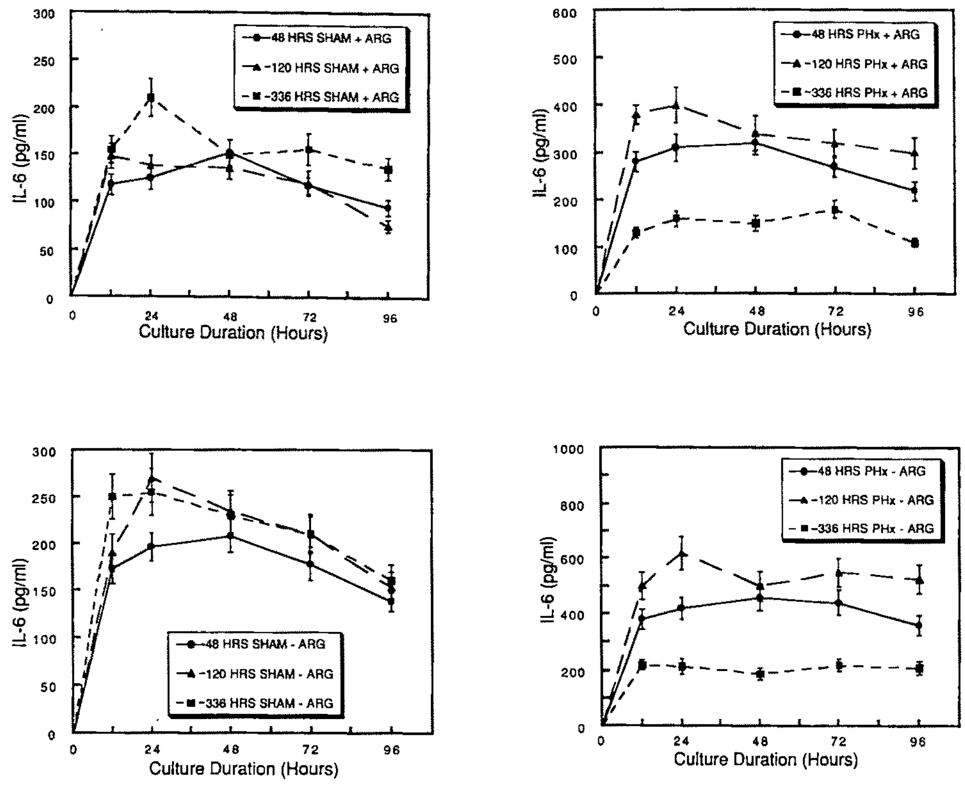

FIG. 1. Kupffer cell IL-6 production by 5×10^5 Kupffer cells after (left) sham-operation or (right) 70% partial hepatectomy in (top) standard RPMI-1640 (1200 μM L-arg) or (bottom) arginine-depleted RPMI-1640 (10 μM L-arg) 48, 120, and 336 hours after operation.

time points in response to LPS stimulation than did equal numbers of Kupffer cells from time-matched sham-operated control animals when cultured in standard (1200 μM L-arginine) RPMI-1640 (Fig. 1). This enhancement of regenerating Kupffer cell production was maximal between 48 and 120 hours after partial hepatectomy and persisted throughout the culture duration (48, 120, and 168 hours) after 70% partial hepatectomy. The depletion of arginine (to 10 μM) from *in vitro* KC cultures, however, resulted in a significant increase ($p < 0.05$ *versus* standard RPMI-1640) in KC IL-6 production, most notably during the first 48 hours of culture (Fig. 1).

To determine whether the observed increase in regenerating liver KC IL-6 production persisted once regeneration of hepatic mass neared completion, the kinetics of IL-6 production by the KC was determined 14 days (336 hours) after both 70% partial hepatectomy and sham operation (Fig. 1). Regenerating KCs no longer produced larger quantities of IL-6 in response to LPS than did equal numbers of sham-operated KCs in either standard or arginine-depleted RPMI-1640 tissue culture media.

Effects of 70% Partial Hepatectomy on KC PGE_2 Production

The production of PGE_2 by 5×10^5 KCs after stimulation with 2.5 μg/mL bacterial LPS was significantly ($p < 0.01$) higher than PGE_2 production by an equal number of time-matched sham-operated KCs, 48, 120, and 168 hours after partial hepatectomy in standard RPMI-1640 tissue culture media (Fig. 2). Because of the significant changes in KC IL-6 production related to arginine concentration, we next measured the affects of arginine availability on KC PGE_2 production in response to LPS. Regenerating Kupffer cells cultured in media depleted of arginine (10 μM) produced an earlier and sustained increase in PGE_2 than did sham KC, with levels reaching 30 ng/mL (Fig. 2). This marked difference in PGE_2 production was no longer present at 336 hours (14 days) after partial hepatectomy, when regenerating KC PGE_2 production had returned to levels comparable to those produced by sham-operated KCs 336 hours after operation.

Effects of PGE_2 on KC IL-6 Production

Prostaglandin E_2 is known to be immunosuppressive and to downregulate the KC's production of tumor necrosis factor-α.[21,22] To test the possibility of an autoregulatory effect by KC PGE_2 production on KC IL-6 production, the cyclo-oxygenase inhibitor indomethacin (1×10^{-5} M) was added to parallel standard RPMI-1640 and arginine-depleted RPMI-1640 cultures. The addition of indomethacin inhibited KC PGE_2 production by >95%.[21] Consequently, with elimination of the inhibitory influences of elevated levels of PGE_2, IL-6 production by both sham-operated and regenerating KCs was signifi-

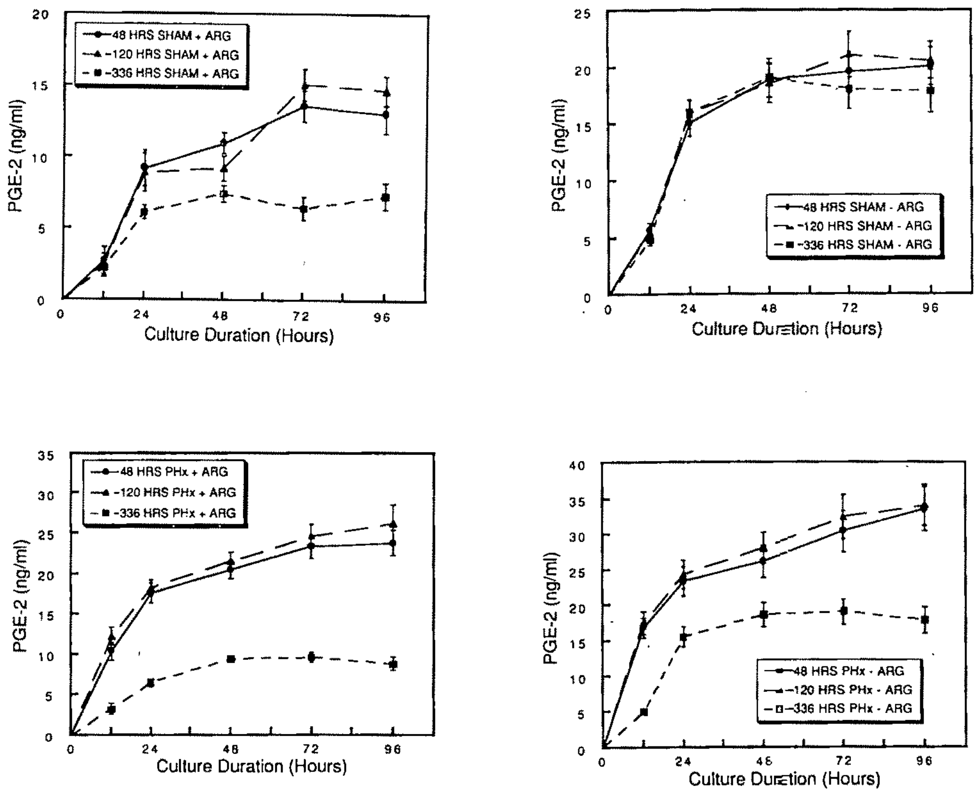

FIG. 2. PGE_2 production by 5×10^5 Kupffer cells after (top) sham operation or (bottom) 70% partial hepatectomy in (left) standard RPMI-1640 (1200 μM L-arg) or (right) arginine-depleted RPMI-1640 (10 μM L-arg) 48, 120, and 336 hours after operation.

cantly ($p < 0.05$) increased in arginine-depleted RPMI-1640 media, but not in standard RPMI-1640 media (representative sham and PHx KC data are presented in Fig. 3).

Effects of PGE$_2$ on Splenic, Peritoneal, and Alveolar Macrophages

To determine whether the regulatory effects of PGE$_2$ on IL-6 was unique to the KC, we measured the IL-6 responses of three macrophage populations in response to LPS stimulation, with and without PGE$_2$ blockade, in both standard RPMI-1640 and arginine-depleted RPMI-1640. Unlike KCs, nonelicited peritoneal macrophages, splenic macrophages, and alveolar macrophages do not normally encounter LPS and function in a microenvironment that is not depleted of L-arginine. When activated by LPS in a 1200-μM arginine culture, sham-operated, peritoneal, splenic, and alveolar macrophages produced low levels of IL-6 and PGE$_2$. After a 70% partial hepatectomy, however, the peritoneal, splenic, and alveolar macrophages all responded to LPS stimulation with elevated production of IL-6 and PGE$_2$ at 48, 120, and 168 hours. In the high-arginine tissue culture environment, inhibition of PGE$_2$ production by the addition of indomethacin did not alter the production of IL-6 by these cell populations. To determine whether these arginine-specific alterations in LPS response were unique to the KC, the peritoneal, splenic, and alveolar macrophages also were cultured in an arginine-depleted environment. With decreased arginine levels, both IL-6 and PGE$_2$ production by these cell populations were all increased. In contrast to the response by the KC, however, the peritoneal, splenic, and alveolar macrophage populations in an arginine-depleted environment did not further increase IL-6 production after blocking the production of PGE$_2$ with indomethacin (representative peritoneal macrophage IL-6 data are presented in Fig. 4. There was no difference in responsiveness between peritoneal, splenic, and alveolar macrophages).

Discussion

Hepatic regeneration in the rat is characterized by an initial 8-hour quiescent period, which is followed by an enhanced hepatocyte DNA synthesis, which is maximal 24 hours after hepatectomy. Rapid cellular proliferation follows this period of increased DNA synthesis and results in almost complete restoration of the liver's original mass within 10 to 14 days of PHx.[1] During hepatic regeneration, new hepatocytes are generated from existing hepatocytes by mitosis, which therefore appears to be a locally controlled process.[1,19] In this study, we demonstrate that the KC, which functions in a unique microenvironment with high arginase and negligible L-arginine levels,[23] and is anatomically juxtaposed with the hepatocyte, and produces

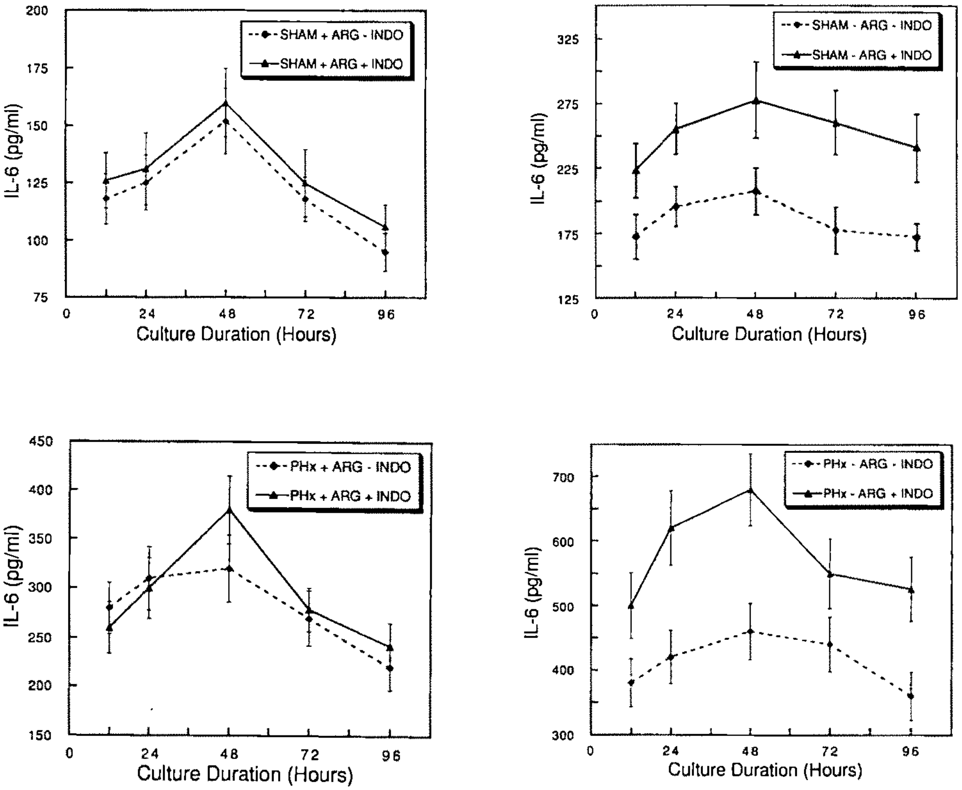

FIG. 3. Effects of 10 μM indomethacin on IL-6 production by 5 × 10^5 Kupffer cells stimulated with 2.5 μg/mL lipopolysaccharide in (top) sham-operated and (bottom) partially hepatectomized rats, cultured in (left) standard RPMI-1640 (1200 μM L-arg) and (right) low-arginine RPMI-1640 (10 μM L-arg).

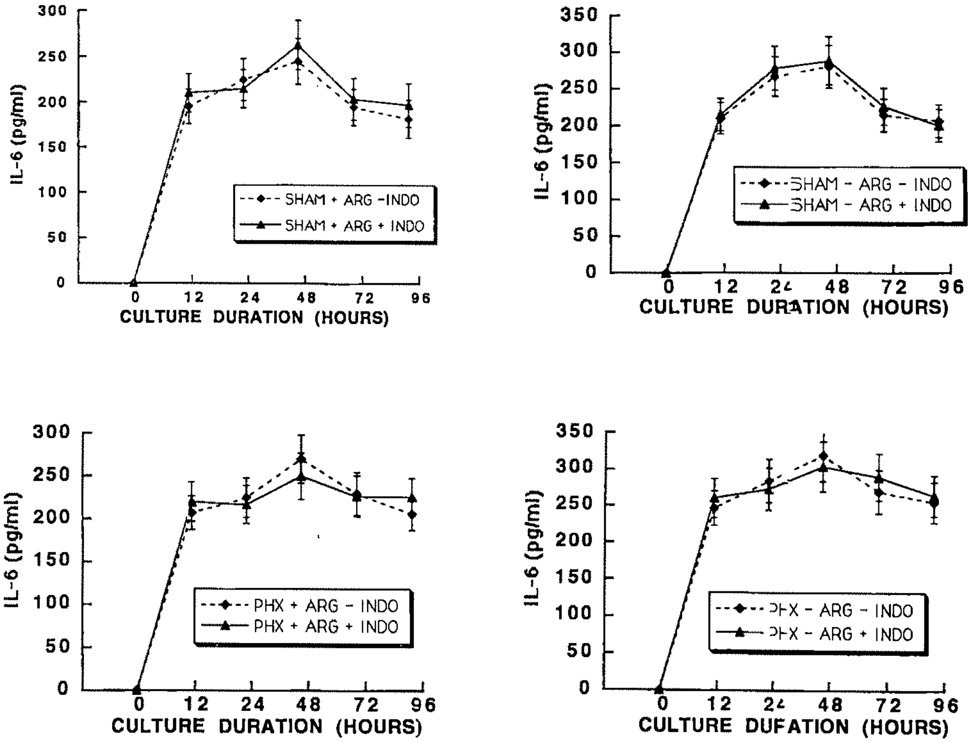

FIG. 4. Effects of cyclo-oxygenase blockade on IL-6 production by 5 × 10^5 peritoneal macrophages stimulated with 2.5 μg/mL lipopolysaccharide in (top) sham-operated and (bottom) partially hepatectomized rats, cultured in (left) standard and (right) low-arginine RPMI-1640.

increased levels of IL-6 and PGE_2 during hepatic regeneration. Because it has previously been shown that KCs and hepatocytes are interdependent during health and illness, this finding leads us to conclude that the KC plays a more central role in hepatic regeneration than previously recognized.[13,14] Cornell[24] has demonstrated that endogenous bacterial LPS, which continuously bathes KCs, accelerates the regenerative process, and that liver regeneration is abrogated when gut-derived LPS is neutralized by polymyxin B or eliminated by chronic lavage with neomycin and cefazolin.

In addition to inducing the acute phase response,[15] IL-6 also activates the maturation of hematopoietic progenitor cells,[25] stimulates B-cell immunoglobulin synthesis,[25] and augments the differentiation of cytotoxic T lymphocytes.[26] During mammalian hepatic regeneration, however, the most important contribution of IL-6 produced by the KC is probably hepatocyte growth,[16] the essence of hepatic regeneration. This demonstration of elevated production of IL-6 by regenerating KCs during the early stages of hepatic regeneration provides additional support to our hypothesis that the cytokines produced locally by the KC play an important role in hepatic regeneration. Prostaglandin E_2 autoregulation of KC IL-6 production would be beneficial to the host because elevated IL-6 production is needed for a short period to induce hepatocyte growth, but if uncontrolled would lead to a state of continuous acute phase response and catabolism detrimental to the health of the host.

The increased amount of PGE_2 produced by the regenerating KC is also a documented mitogenic stimulus for hepatocytes.[27,28] Evidence that this potent paracrine growth factor could stimulate enhanced DNA synthesis and proliferation of neighboring hepatocytes within the regenerating liver is further supported by the time course of PGE_2 production during hepatic regeneration (Fig. 2). Because KC PGE_2 production is elevated during the induction and maximal regenerative response of the remaining hepatocytes, locally produced PGE_2 would qualify as a theoretical hepatic regeneration initiation substance. That this amplified KC PGE_2 response subsequently subsides as the hepatic mass returns to its original size and regeneration ceases provide additional support for the hypothesis that regenerative KCs produce PGE_2, which stimulates DNA synthesis and the proliferation of neighboring hepatocytes. More importantly, our finding that the KC uniquely controls its own IL-6 production through PGE_2, unlike other macrophage populations, may reflect an evolutionary adaptation of KCs to their position in the portal venous circulation to directly minimize the local and systemic adverse effects of gut-derived endotoxin. As specialized macrophages in an arginine-depleted microenvironment, the KCs are unique because they normally and continuously sequester the small quantities of LPS, which penetrate the intact gastrointestinal mucosal barrier and drain directly into the portal circulation.[11] Therefore, the kinetics of IL-6 and PGE_2 production by the regenerating KC with bacterial

LPS stimulation[24] and the known importance of IL-6 and PGE_2 on *in vitro* hepatocyte proliferation indicate the central importance of the Kupffer cell in this unique mammalian response.

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Discussion

Dr. Robert Zeppa (Miami, Florida): Dr. Bland, Dr. Jones, colleagues, I am indebted to Dr. Flye for his invitation to discuss this paper under the assumption that I know something about cytokines. That is in error. I think Wayne asked me to comment on this because 20 years ago Joe Levi and I were studying the regenerative problem of rodent liver. And, of course, in paired *in situ* perfused animals, we discovered that at 24 hours, as Dr. Flye has pointed out, there came into the circulation media some substance that we were never able to characterize, which had an effect on normal liver if they were cross-circulated, in that DNA synthesis went up at that 24-hour period in both livers. That is by way of some historical background. But what I would like to ask Dr. Flye about these experiments is, if in fact the animals are pretreated with indomethacin, what happens then to your pellet of Kupffer cells? This is fascinating and reminds me a little of the presentation that Dick Simmons gives in which he calls it "pillow talk in the liver," that is, the communications between the Kupffer cells and the hepatocytes, which appear now more and more, thanks to the work of Dr. Flye and his group, to be one of the most important factors that we have in terms of how the liver responds to a variety of stimuli, not merely regeneration. Thank you.

Dr. Courtney M. Townsend, Jr. (Galveston, Texas): Dr. Bland, Dr. Jones, Fellows and Guests, Dr. Flye and his colleagues have long been interested in the problem of hepatic regeneration and the interaction of immunologically competent cells with hepatocytes. This study, I think, provides more information into the mechanisms by which Kupffer cell functions are regulated. It appears that there is a tight autocrine control, at least of prostaglandin, on interleukin-6 (IL-6) production.

What are the signals that are at play here? That is, what turns the Kupffer cells on to begin increasing their responsiveness to make IL-6 in response to lipopolysaccharide? Also, does a reciprocal relationship exist? That is, if you were to decrease IL-6, would you increase prostaglandin production? And is there any evidence that exogenously added prostaglandin would further affect the level of IL-6 produced? And, finally, do you know whether the mechanism of action of prostaglandin on IL-6 production is direct or indirect? And if it is indirect, what possible second messengers are involved? Thank you very much.

Dr. George Parker (Richmond, Virginia): Dr. Bland, Dr. Jones. Like Dr. Zeppa, I am not sure why I was asked to discuss this paper. I think the only reason is that 19 years ago Wayne Flye was my first senior resident when I was an intern, and he still treats me the same. I have a couple of questions and a couple of comments.

The comment would be I think it is a very elegantly designed and carried out study with all the proper controls, so I think the data are incontrovertible.

The first question I would have is, do you have any idea if the amount of interleukin-6 that is being produced would be sufficient to induce hepatocyte stimulation and mitosis? Second, you mentioned about the factors of the Kupffer cell inducing regeneration or helping in the regenerative process. What is different about certain injuries where there is just fibrosis *versus* certain injuries where there is regeneration? And would you speculate on the possible role of the Kupffer cell there? Thank you very much.

DR. WAYNE FLYE (Closing discussion): I would like to thank the discussants. Dr. Zeppa, you and Dr. Bernard Fisher earlier performed pioneering work in liver regeneration. Obviously, this is a much more complex phenomenon than can simply be explained by the effect of cytokines. Cytokines appear to regulate, more than initiate, regeneration. If you add PGE_2 to hepatocytes in culture, you can get increased DNA proliferation. Addition of indomethacin blocks prostaglandin synthesis and retards the course of liver regeneration. High doses of PGE_2 in vivo will result in diarrhea and animal death.

Dr. Townsend, you ask what signals are important for regeneration. In vitro addition of interleukin-6 downregulates prostaglandin E_2 production, as does tumor necrosis factor and interleukin-1. This may be effected by activation of phospholipase A2 and the mobilization of fatty acids and arachidonic acid from the cell surface. We know that PGE_2 is an important regulator of cell proliferation, probably by increasing cyclic adenosine monophosphate (cAMP) levels. When we infuse the long-acting 16,16 dimethyl PGE_2, which is not metabolized on first passage through the lung, as are most natural prostaglandins, into a heterotopic heart allograft continuously for 2 weeks, we completely prevent graft rejection. We know that the early recognition phase of rejection is related to how the macrophage presents antigen to effector lymphocytes. We have evidence that the migration of lymphocytes and macrophages through the graft are impaired by PGE_2. Although liver regeneration is a different phenomenon, the mechanism of regulation of second signals is probably similar. Changes in interleukin-6 levels do not cause changes in PGE_2 production, whereas exogenous PGE_2 does decrease interleukin-6 levels.

Although the Kupffer cells are probably normally exposed to low levels of endotoxin, it is only during exposure to higher levels that Kupffer cells significantly increase PGE_2 and cytokine production, *i.e.*, during bacteremia and during the stress of liver regeneration. However, R. P. Cornell has shown that neutralization of the lipid A portion of endotoxin with polymyxin B in normal animals slows liver regeneration. The levels of PGE_2 produced by the Kupffer cells appear adequate to regulate the adjacent hepatocytes.

Dr. Parker, the fibrotic liver does not regenerate well. This is clinically important in the patient with cirrhosis undergoing liver resection. The hepatocyte within the milieu of the fibrotic tissue behaves differently than when it can function in a normal hepatic environment.

I would like to thank the discussants for their remarks and the Association for the privilege of presenting this work.

The Zollinger-Ellison Syndrome

A Collective Surgical Experience

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A retrospective study of 90 surgically treated patients with the Zollinger-Ellison syndrome seen from 1958 through 1990 was performed. Fifteen patients had Zollinger-Ellison syndrome as a manifestation of multiple endocrine neoplasia type I. Preoperative tumor localization was positive in 46% of 54 patients studied. Gastrinomas were identified in 66% of patients, 38% of the tumors being malignant. Postoperative eugastrinemia was achieved in 11% of patients after a variety of surgical procedures. Exploratory laparotomy provides the only chance for cure and identifies the significant prognostic factors associated with long-term patient survival: small tumor size, extrapancreatic primary, and absence of tumor metastases.

ALTHOUGH DOCTORS ZOLLINGER and Ellison uncovered the mystery of hypergastrinemia with their epoch publication in 1955, which recommended total gastrectomy for effective therapy,[1] multiple improvements in radiographic imaging, pharmacologic therapy, and surgical techniques in the ensuing three decades have made the current treatment of patients with Zollinger-Ellison syndrome (ZES) controversial.

Historically, it was believed that tumor excision for cure was possible in only 2% to 5% of patients.[2-4] Understandably, with the introduction of pharmacologic agents that essentially shut off gastric acid secretion (histamine-receptor [H_2] blockade in 1976 and blockage of the H^+-K^+ adenosine triphosphatase pump with omeprazole in 1984), some authorities recommended medical therapy in place of surgical treatment for patients with ZES.[3]

Coupling the initial development (1968)[5] and subsequent improved accuracy of gastrin radioimmunoassay with a heightened physician awareness of ZES, patients are currently seen earlier in the course of their disease. Development of potent antisecretory agents increased the enthusiasm for resection of tumor with the aim of achieving permanent cure and avoiding lifelong drug therapy with its associated costs and possible side effects (Table 1). Currently, careful search and removal of gastrinomas has yielded putative cure rates in 30% to 53% of selected patients.[6-8]

The present study was undertaken to assess our experience with the changing surgical and pharmacologic management of patients with ZES and to delineate factors significant for long-term survival.

Patients and Methods

Of 156 patients with well-characterized ZES seen at the Mayo Clinic from 1958 through 1990, 90 patients undergoing surgical exploration form the basis of this retrospective report. Sixty-six patients were excluded from this study because of nonoperative management: 33 with extensive hepatic metastases were deemed unresectable, 20 refused operative management, 9 with the multiple endocrine neoplasia type I (MEN-I) syndrome and asymptomatic on medication had multicentric pancreatic involvement and thus operative therapy was deferred, 2 were refused operation because of prohibitive anesthetic risk, and 2 asymptomatic patients with MEN-I syndrome were believed not to be candidates for operation at that time.

Factual data of the 90 surgical patients was obtained regarding presenting symptomatology, diagnostic and laboratory evaluation, operative intervention, postoperative morbidity and mortality rates, pharmacologic ther-

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TABLE 1. *Cost of Pharmacologic Control of Zollinger–Ellison Syndrome*

Drug	Average Effective Daily Dose (mg)*	Yearly Cost†
Cimetidine	3600	$3714.12
Ranitidine	1200	$2514.36
Famotidine	250	$5714.59
Omeprazole	80–90	$5008.42

* Data from Maton et al. Gastroenterol Clin North Am 1989.

† Calculated wholesale cost ordering bulk amounts to Mayo Pharmacy in 1991.

TABLE 2. *Presenting Symptoms*

Symptom	No. of Patients (%)
Epigastric pain	84 (93)
Diarrhea	46 (51)
Dizziness	2 (2)
Weight loss	1 (1)
Abdominal mass	1 (1)

apy, and long-term follow-up. Current survivors were contacted by telephone or were seen for physical examination within the past year (through January of 1991).

The diagnosis of ZES was confirmed in each patient based on at least two of the following criteria:

1. History of severe peptic ulcer disease or unexplained diarrhea
2. Fasting serum hypergastrinemia (>200 pg/mL) or markedly elevated gastric acid output (>15 mmol HCl/hour)
3. Positive secretin-stimulated gastrin analysis (increase in serum gastrin of > 200 pg/mL after intravenous injection of 2 units secretin/kilogram of body weight)
4. Histologic confirmation of a neuroendocrine tumor

Analysis of discrete and continuous variables was performed using the log rank test[9] and Cox's proportional hazards model,[10] respectively. Estimates of survival for the study group and an age- and sex-matched control population (1980 North Central United States) were compared using the method of Kaplan and Meier.[11] Multivariate associations of survival were investigated using the model of Cox.[10]

Results

Epidemiology

Surgical exploration was performed in 59 men and 31 women. Operative candidates ranged in age from 13 to 72 years (mean, 51 years). Sporadic disease occurred in 75 patients (83%), whereas 15 patients (17%) had hypergastrinemia as a manifestation of the MEN-I syndrome.

Symptoms

Patients presented with an array of physical complaints (Table 2) at the time of diagnosis, with a median duration of symptoms of 2 years (mean, 3.2 years; range, 2 months to 18 years). On presentation to the Mayo Clinic, most patients were on pharmacologic therapy for peptic ulcer disease or diarrhea: antacids (49%), H_2 antagonists (28%), omeprazole (4%), somatostatin (2%), or streptozotocin (1%). Only 14 patients (16%) were not taking medication.

Laboratory Analysis

Preoperative gastric acid analysis (n = 15) disclosed a mean basal acid output of 40.2 mmol HCl/hour (range, 11.0 to 90.0). The average pH of a preoperative gastric aspirate was 1.29 (range, 0.9 to 2.4).

Before abdominal exploration, baseline serum gastrin values ranged from 140 to 21,000 pg/mL (mean, 2357 pg/mL; Mayo normal range, 0 to 200 pg/mL). Of 31 patients tested by secretin stimulation, including two patients with normal baseline levels, all had serum gastrin elevations of >200 pg/mL within 20 minutes after injection.

Preoperative Radiographic/Endoscopic Evaluation

Upper gastrointestinal barium radiography or esophagogastroduodenoscopy delineated extensive peptic ulceration in 91% of patients. Since the advent of H_2 receptor blockade, less than 70% of patients have evidence of peptic ulceration, and even then, ulceration is minimal, with only minor mucosal changes. Duodenal ulceration was detected in 63 patients, jejunal ulceration in 9, and 10 patients had peptic ulceration in both locations. Eight patients had no evidence of peptic ulceration. Fifty-four patients underwent further evaluation to attempt to identify the location of the primary tumor or evidence of metastasis. Preoperative localization of the *primary* gastrinoma was successful in only 25 of these 54 patients (46%) (Table 3).

TABLE 3. *Diagnostic Imaging of Gastrinomas in Patients With Zollinger–Ellison Syndrome*

	No. of Patients	Primary Identified No. (%)	Metastasis Identified
Computed tomography	40	13 (33)	7
Angiography	20	1 (5)	2
Preoperative ultrasonography	19	7 (36)	0
Magnetic resonance imaging	11	4 (36)	4
Intraoperative ultrasonography	10	6 (60)	1
	54	31 (57)	14

Intraoperative Localization

Surgical identification, or confirmation by palpation, of the primary gastrinoma occurred in 53 patients (59%). The use of intraoperative ultrasonography imaged nonpalpable tumors in six additional patients (7%). Thus, of the 90 patients, primary tumor was *first* identified by preoperative imaging in 25 (28%), by intraoperative palpation in 28 (31%), and by intraoperative ultrasonography in 6 (7%). A primary tumor was, therefore, not identified in 31 patients (34%), although 7 such patients had identifiable metastatic disease (lymph nodes 5, liver 2). Thus, in 24 patients (27%), most of whom were operated on long before thorough duodenal evaluation was standard procedure, the potentially curable gastrinoma was never identified.

Pathology

Primary gastrinomas were identified pathologically in 59 patients (66%) (Table 4). Fifty such tumors were located within the gastrinoma triangle, including 13 duodenal tumors (Fig. 1). Tumor size ranged from 0.2 to 12 cm in largest diameter (mean, 3.1 cm; median, 2.5 cm). Metastatic involvement was documented in 34 patients (38%). A single patient was found to have focal multiple microadenoma (nesidioblastosis) and was treated by radical pancreatoduodenectomy.

Operative Management

Before evaluation by us, 20 patients (22%) had at least one previous operation performed elsewhere (as many as four procedures) for peptic ulceration. A wide array of operative procedures were performed on this heterogeneous group of patients at our institution over the 33 years surveyed (Table 5). Five procedures were done on an emergency basis (only one since 1976). A total of 12 patients underwent surgical re-exploration by us for recurrent symptoms of ZES after their initial procedure (Table 6). Two patients with metastatic disease subsequently required bilateral adrenalectomy for control of Cushing's syndrome related to ectopic adrenocorticotropic hormone production by the islet cell tumor. A single patient had enucleation of two pancreatic gastrinomas (removed elsewhere) 20 years after total gastrectomy had been performed by us.

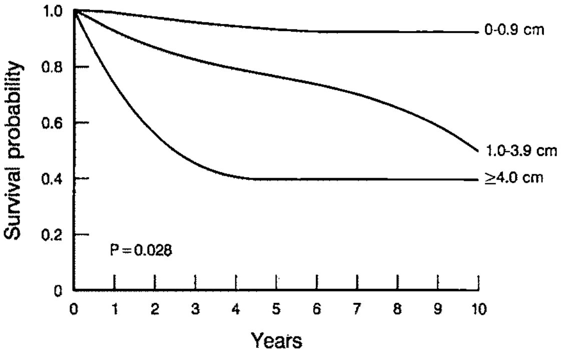

FIG. 1. Location of primary gastrinoma (n = 90) in relation to the gastrinoma triangle.

TABLE 4. *Tumor Involvement in Patients With Zollinger-Ellison Syndrome*

Primary Tumor Location	Sporadic	MEN-I
Pancreas (n = 42)		
Head	12	0
Body	11	0
Tail	6	0
Uncinate	1	0
Multiple sites	6	6*
Duodenum (n = 13)	12	1
Stomach (n = 3)	2	1
Retroperitoneum (n = 1)	0	1
Unknown primary (n = 31)	25	6
	75	15
Metastases (n = 34)		
Lymph nodes	10	4
Hepatic	19	1
Adrenal†	2	0
Pulmonary†	2	0
	33	5

* Two patients had synchronous duodenal tumors.
† All four patients also had hepatic metastases.

Although 40 patients had total gastrectomy performed at the Mayo Clinic, only three such procedures have been

TABLE 5. *Operative Management of Zollinger-Ellison Syndrome*

Initial Mayo Procedure	No.
Total gastrectomy	22
Total gastrectomy + distal pancreatectomy	4
Total gastrectomy + enucleation	3
Total gastrectomy + hepatic metastasis excision	1
Distal pancreatectomy	11
Distal pancreatectomy + enucleation, distal pancreatectomy + vagotomy, distal pancreatectomy + intraoperative radiotherapy, distal pancreatectomy + hepatic metastasis excision	
Enucleation	13
Whipple procedure	4
Miscellaneous	
Tumor biopsy	8
Partial gastrectomy	4
Truncal vagotomy	3
Partial gastrectomy + vagotomy	2
Right hepatectomy, hepatic dearterialization, palliative gastrojejunostomy, palliative cholecystojejunostomy, left nephrectomy + tumor biopsy, aortofemoral bypass graft + duodenotomy	1 each
Emergency procedures	
Total gastrectomy	2
Vagotomy + pyloroplasty	1
Biopsy	1
Partial gastrectomy + vagotomy	1
Total	90

TABLE 6. *Follow-up Operative Procedure for Patients With Symptoms of Zollinger-Ellision Syndrome*

Age	Sex	MEN-I	Initial Procedure	Time Lapse	Secondary Procedure
54	M	No	Distal pancreatectomy	5.0 mo	Enucleation
54	M	No	Enucleation	7.5 yr	Total gastrectomy
52	F	No	Whipple procedure	1.3 yr	Total gastrectomy + hepatic metastasis excision
60	M	No	Partial gastrectomy	11.0 yr	Tumor biopsy
48	F	No	Partial gastrectomy	2.6 yr	Total gastrectomy
50	M	No	Partial gastrectomy	4.3 yr	Total gastrectomy
46	F	No	Truncal vagotomy*	14.0 days	Total gastrectomy
57	M	No	Partial gastrectomy + truncal vagotomy	1.0 mo	Partial gastrectomy
41	F	No	Distal pancreatectomy	1.0 yr	Right hepatectomy
44	F	No	Total gastrectomy	20.0 yr	Enucleation†
36	F	Yes	Truncal vagotomy	3.0 mo	Total gastrectomy
49	F	Yes	Distal pancreatectomy	6.0 mo	Total gastrectomy
41	M	Yes	Enucleation	9.5 yr	Total gastrectomy

* Emergency procedure.

† Performed elsewhere.

performed on ZES patients since 1977, and just one since 1980. Five of 23 ZES patients with an intact gallbladder after total gastrectomy subsequently required cholecystectomy for symptomatic cholelithiasis.

Hospitalization

Patients were hospitalized an average of 17 days (range, 2 to 70 days; median, 13). Twenty-four patients (27%) had 30 postoperative complications (Table 7). Three patients required reoperation related to postoperative complications (gastric bleeding, small bowel obstruction, and jejunojejunostomy leak). Overall 30-day operative mortality rate was 4%.

Follow-up

Fifty-one patients remain alive at an average of 11 years after initial operation. Ten patients (11%) remain eugastrinemic off all medication, ranging from 1 to 17 years after surgical excision of the primary gastrinoma (duodenum, 6; stomach, 3; pancreatic head, 1). Of five patients tested, four have normal postoperative secretin-stimulated levels. Twelve patients refrain from medication but have intermittent symptoms of gastric hypersecretion (epigastric pain or diarrhea). The remaining 29 patients are asymptomatic on medication.

Cause of death in 39 patients was due to tumor progression (24), postoperative deaths (4), peptic ulcer disease (2), and non-ZES related deaths (9). Overall 5- and 10-year survival for the study group was 76% and 68%, respectively. Five- and 10-year survival for an age- and sex-matched control population was 93% and 88%, respectively.

Prognostic Factors for Survival

Patient outcome (long-term survival) correlated significantly with primary tumor size, primary tumor location, and degree of tumor involvement (Table 8). Significant prognostic factors were important at both 5- and 10-year intervals (Figs. 2, 3, 4).

TABLE 7. *Postoperative Complications in 24 Patients*

Complication	No.
Symptomatic peptic ulcer disease	4
Gastrointestinal bleeding	4*
Wound infection	4
Ileus	4
Pneumonia	3*
Urinary tract infection	3
Small bowel obstruction	2
Esophagojejunostomy leak	2
Myocardial infarction	1*
Jejunojejunostomy leak	1
Intra-abdominal abscess	1
Sepsis	1*
Total	30

* Postoperative deaths.

TABLE 8. *Long-term Survival: Prognostic Factors*

Variable	p (n = 90)	p (MEN-I, n = 15)
Attempted surgical cure	0.972	0.982
Baseline preoperative gastrin level	0.183	—
Date of operation (before 1977 *vs.* after 1977)	0.385	0.170
Emergency *vs.* elective procedure	0.186	—
Sex	0.135	0.289
MEN-I *vs.* sporadic	0.927	—
Metastatic involvement	0.0004*	0.372
Patient age	0.451	0.229
Tumor location	0.006*	0.527
Tumor size	0.028*	0.667
Type of operative procedure	0.390	0.932

* $p < 0.05$.

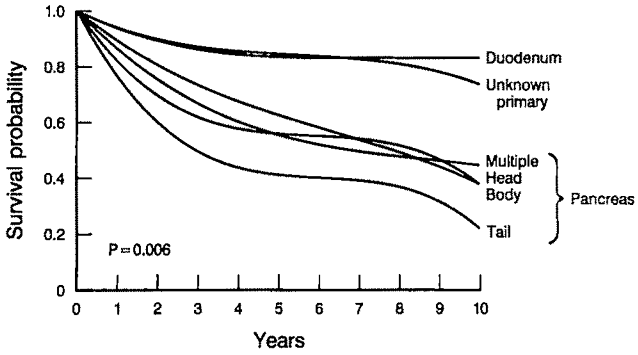

FIG. 2. Correlation of primary tumor location (n = 90) with long-term survival.

Multiple Endocrine Neoplasia Type 1

The 15 patients with ZES as a manifestation of MEN-I had a variety of pathologic lesions and subsequently underwent varied surgical management. Gastrinomas were identified in nine patients (multicentric in pancreas, 4; multicentric in pancreas and duodenum, 2; duodenum, 1; retroperitoneum, 1; and stomach, 1) (Table 4). Three such patients had metastatic involvement (lymph nodes, 2; liver, 1). Six patients had no primary gastrinoma identified, although a single patient did have metastatic nodal disease.

Surgical management consisted of total gastrectomy (5), tumor enucleation (3), partial gastrectomy (2), distal pancreatectomy (2), truncal vagotomy (2), and tumor biopsy (1). Postoperative complications were minimal (wound infection, 2; pneumonia, 1; urinary tract infection, 1), with no postoperative deaths. Three patients required reoperation for persistent peptic ulcer disease (Table 6). Eight patients remain alive. Deaths were attributable to tumor progression (2), peptic ulcer disease (1), and non–ZES-related deaths (4). No patient was rendered eugastrinemic despite six patients who underwent duodenotomy with excision of a duodenal gastrinoma in three.

Significant prognostic factors (Table 8) were not identified for this subset of 15 patients with MEN-I. Long-term survival of MEN-I patients was, however, equivalent to that of patients with sporadic disease.

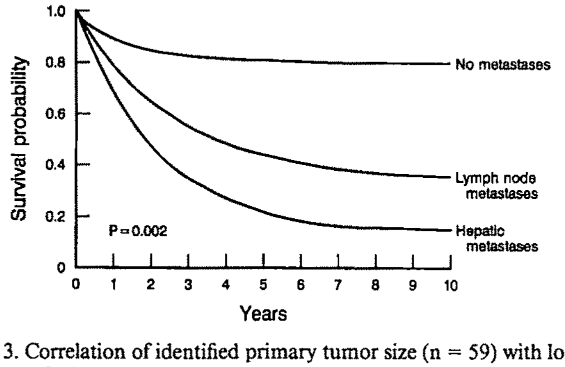

FIG. 3. Correlation of identified primary tumor size (n = 59) with long-term survival.

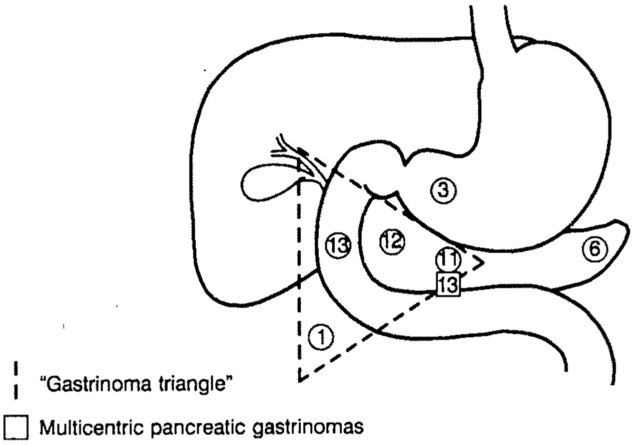

FIG. 4. Correlation of overall tumor involvement (n = 90) with long-term survival.

Total Gastrectomy

A total of 40 patients (24 men, 16 women; average age, 48 years) underwent total gastrectomy as either a primary or secondary procedure (Tables 5 and 6) to specifically control the symptoms of ZES. Ten patients (25%) incurred major complications (anastomotic leak, 3; intra-abdominal abscess, 2; prolonged ileus, 2; sepsis, 2; small bowel obstruction necessitating reoperation, 1; gastrointestinal bleeding, 1; and myocardial infarction, 1). Two patients died as a direct result of postoperative complications (5% operative mortality rate). Average duration of hospitalization was 20 days (range, 8 to 70 days). Twenty-one patients remain alive at an average of 16.5 years after total gastrectomy. Diarrhea remains problematic in four patients, whereas the remainder of this group has stopped all usage of pharmacologic therapy.

Of the 19 deaths in this group, 12 deaths resulted from tumor progression, five from unrelated causes, and two from complications of the procedure.

Discussion

The epidemiologic data of patients with ZES have been fully elucidated.[12] With a slight male predominance existing, identification of ZES may occur in early childhood through octogenerians.[13] Roughly 75% of patients have sporadic disease, whereas the remaining one fourth of patients have hypergastrinemia as a manifestation of MEN-I. Our study group "conforms" to these epidemiologic norms.

Epigastric pain predominates in patients with ZES and is usually the impetus for patients to seek medical advice. Ellison and Wilson[14] found in a review of a collective registry in 1964 that over one half of the patients had ulceration of the duodenal bulb, whereas 26% had ulceration of the esophagus or jejunum. Severe diarrhea was a prominent symptom in 36% of patients and the sole symptom in 7%. The symptom complex of the current study group is quite similar, with a long prelude before the diagnosis of ZES (as long as 18 years in one patient).

Serum gastrin quantification (baseline and secretin-stimulated) has proven extremely effective since the development of a gastrin radioimmunoassay in 1968.[5] However, false-negative results as high as 10% have been recorded with secretin stimulation by some authors,[15–17] and baseline fasting serum gastrin levels have been reported to be nondiagnostic in more than 50% of ZES patients.[15] From our admittedly select group of patients, only two had normal preoperative serum baseline gastrin values (<200 pg/mL), although 30% had values less than 500 pg/mL. All 31 patients tested did have a serum gastrin rise of >200 pg/mL within 20 minutes of secretin injection.

When a thorough history and physical examination raises the suspicion of ZES, confirmation should be obtained by documenting the presence of hypergastrinemia and by demonstrating a rise in serum gastrin levels of >200 pg/mL after secretin stimulation (positive secretin test). If gastric analysis is done, the usual findings are an increased volume of gastric secretion (8 to 12 L/24 hours), increased basal acid secretion (>15 mmol/hr), and a ratio of basal *versus* stimulated (pentagastrin) acid secretion of more than 60%.

Currently, there are essentially four issues that continue to provide fuel for heated debate whenever ZES is discussed:

1. How may tumor localization be improved on both before and during operation?
2. Is the currently available, extremely effective medical therapy preventing potentially curable patients the benefit of surgical exploration?
3. What is the current role of total gastrectomy?
4. Is the nihilistic surgical attitude concerning patients with MEN-I justified?

Tumor Localization

The ability to localize the primary tumor and detect any liver metastases before operation maximizes the surgeon's ability to care for the ZES patient. As physician awareness and suspicion of ZES increases and laboratory analysis improves, gastrinomas causing ZES are being detected at an earlier stage and thus are becoming more difficult to image. In concert with the present series, 30% to 50% of primary gastrinomas have not been detected before operation by radiographic analysis.[18] Controversy persists regarding the optimal strategy of tumor localization.

Preoperative computed tomography with intravenous and gastrointestinal contrast, coupled with intraoperative ultrasound in selected cases, is our method of choice (for localization). The usefulness of computed tomography scanning to detect hepatic metastases (≥1 cm) or primary gastrinomas (≥1 cm) is proven.[19,20] The accurate resolution to delineate microgastrinomas (<5 mm) is often unobtainable, although intra-abdominal resolution with CT is currently superior to that obtained with magnetic resonance imaging.[21]

Intraoperative ultrasonographic examination of the pancreas and liver is well accepted.[22,23] Sensitivity is high, but specificity remains low for primary gastrinomas.[22] Numerous cures of resected pancreatic-, gastric-, and duodenal-based gastrinomas found by intraoperative ultrasound have been reported.[22,23] We use intraoperative ultrasound routinely, particularly when a primary tumor is not identified and clinical suspicion of a pancreatic gastrinoma remains high. Although we have not used intraoperative endoscopic ultrasound, it may prove to be a useful adjunct to tumor localization in selected cases.[22]

Vinik and co-workers[24] have used selective portal venous sampling as a means to regionalize gastrinomas, with impressive results. Others have been less enthusiastic about this invasive technique.[25] We have little experience with this method of regionalization, believing that the procedure is invasive, expensive, and with results that are extremely variable.

Angiography is thought by many to be the most sensitive study to locate gastrinomas.[26] Although used frequently in the 1970s, our inability to consistently locate the primary gastrinoma with this invasive technique has made simple angiography virtually obsolete for ZES evaluation at the Mayo Clinic. Since the study's completion, we have used digital subtraction angiography with some success, and this new modality warrants further evaluation.

Although less invasive and technically easier to perform than portal venous sampling, the technique of selective arterial secretin injection provides regionalization equivalent to portal venous sampling for pancreatic gastrinomas without false-positive studies.[27–29] Although we have not adopted this newer modality, some authors believe that the combination of angiography and selective arterial secretin injection is the localization procedure of choice for gastrinomas.[30] This innovative technique should be evaluated with a larger clinical experience.

We have been disappointed with our ability to localize, and resect for cure, gastrinomas in patients with ZES. Although we are currently re-evaluating our approach to preoperative and intraoperative localization, we have been encouraged by recent reports of new localizing techniques.

The *in vitro* demonstration of somatostatin receptors by Reubi et al.[31] led to the labeling of octreotide with ^{123}I for scintigraphy. Although radionuclide scanning with this compound was successful in the demonstration of extra-abdominal neuroendocrine tumors, its applicability to evaluation of the pancreas is limited by intense hepatobiliary excretion of the compound.[32] An exciting new agent (^{111}In-DTPA-D-Phe), generically termed ^{111}In-labeled Pentatreotide, appears to have overcome the limiting features of ^{123}I-octreotide.[33] Krenning et al.[33] have reported a 100% success rate in detecting primary gastrinomas in 10 patients with ZES. If the initial promising reports with Pentatreotide continue to be validated with increased clinical experience, we may indeed be entering into yet another exciting episode in the search for the at times elusive gastrinoma.

Currently, however, despite an array of localization techniques before and during operation, nearly 50% of all abdominal explorations in patients with ZES may prove negative for tumor.[34] A thorough and diligent visual and palpatory search by surgeons educated in the intricacies of ZES remains paramount to improving operative success.

Pathologic Localization

Gastrinoma is the second most common neuroendocrine tumor of the abdomen.[2,35] Most of these tumors are reported to occur in the pancreas; however, there are no gastrin-producing cells within the normal adult pancreas. Some authors have suggested that most gastrinomas are, in fact, not within the substance of the pancreas, but lie in the immediate vicinity (*i.e.,* extrapancreatic tissue including the duodenum, stomach, lymph nodes, etc.).[36] Indeed, the absence of immunoreactive gastrin in resected pancreatic tumors in patients with MEN-I has led to intensified surgical exploration for extrapancreatic gastrinomas.[37-39] Duodenal gastrinomas are being recognized with increasing frequency, as knowledgeable surgeons search for these small tumors.[40-42]

No matter which organ is involved, roughly 80% of all gastrinomas identified are contained within the "gastrinoma triangle" as defined by Passaro and others (Fig. 1).[19,43] Of the 59 primary tumors identified in this study, 50 (85%) were located within the gastrinoma triangle. Of the 13 duodenal tumors discovered (26%), nine were identified since 1976. Unfortunately, absence of identifiable primary tumor occurred in 31 patients (34%), which parallels other reports.[4,44] Encouragingly, more recent studies have identified tumors in more than 85% of patients.[19,45]

Differentiating benign from malignant gastrinomas histologically is virtually impossible. Roughly 60% of gastrinomas are malignant.[14] Until histologic differentiation is perfected, malignancy is dependent on tumor extension beyond the primary organ (*i.e.,* nodal or hepatic metastases). Although only 38% of the study group had evidence of malignancy, future follow-up will likely uncover tumor progression (malignancy) in additional patients.

Operative Management

With the advent of effective gastric-acid antisecretory medication, the focus of operative management has shifted from control of hypersecretion to tumor resection. Surgical resection remains the best therapy for ZES, because over half of patients with unresected tumor die of their disease.[12,41]

Aggressive attempts to resect tumor for cure are warranted. We have, in fact, performed pancreaticoduodenectomy for a single well-differentiated gastrinoma in the head of the pancreas (unable to be enucleated) in three separate patients with sporadic ZES. A fourth patient was similarly treated for localized multiple microadenoma (nesidioblastosis), a resection that rendered the patient eugastrinemic. Likewise, resection of a hepatic metastasis was performed in conjunction with resection of the primary tumor in a single patient. Although none of these patients sustained postoperative complications, four of the five remained hypergastrinemic. Although discouragingly low, a total of 10 patients (11%) were "cured" by surgical resection, representing a 34% cure rate of the 29 bona fide attempts at complete tumor removal. Not surprisingly, six of 13 patients (46%) with duodenal gastrinomas were rendered eugastrinemic. As the surgical management of ZES has evolved over the past 33 years, now including thorough evaluation of the duodenum as standard practice, we trust that curative resections will increasingly become commonplace.

For patients with an unknown tumor burden, widely metastatic disease, or the MEN-I variety of ZES, we have been less aggressive surgically. With effective antisecretory medication currently available, we do not feel justified in subjecting these patients to the risks of total gastrectomy or partial pancreatectomy without tumor control. Total gastrectomy for most ZES patients, however, has been advocated by some.[4,46,47] In a young patient adverse to medical therapy or who may be difficult to follow, total gastrectomy remains a good treatment option. In such an instance, cholecystectomy appears warranted at the time of total gastrectomy.[48] After total gastrectomy, five of our patients eventually required cholecystectomy for symptomatic biliary tract disease. We believe that the indications for total gastrectomy are today extremely rare.

Patients with MEN-I and ZES have not been curable in most reports because of tumor multicentricity.[7,24,25,49,50] Although an attitude of surgical nihilism is omnipresent for MEN-I patients with ZES, it is interesting that

Thompson et al.[42] and Pipeleers-Marichal et al.[39] have recently reported "cures" after extensive exploration and subsequent removal of multiple duodenal microgastrinomas (<5 mm). Their surgical approach has employed duodenotomy with excision of one or more microgastrinomas, routine removal of paraduodenal and peripancreatic lymph nodes (many of which will contain metastatic disease), and a distal pancreatectomy. This exciting work warrants careful attention.

Similarly, Tisell et al. have suggested total pancreatectomy in highly selected MEN-I patients to maximize the chance of surgical cure.[51] In MEN-I families with a history of aggressive pancreatic malignancies, this approach may be warranted.

Pharmacologic therapy in MEN-I patients is effective, but in patients with uncontrollable symptoms, some[34] have advocated parietal cell vagotomy to be a viable option when no tumor is found. Although we have not performed PCV in this setting, the procedure has been shown to reduce gastric acid secretion (and hence H_2 antagonist requirements) by approximately 40% in patients with ZES.[34] The advent of omeprazole has, in all probability, rendered this surgical option obsolete.

Survival

Although the 5-year survival for ZES patients with resectable primary tumor is virtually 100% (whether resected or not),[52,53] patients with unresectable disease have a poor outcome (5-year survival, 43%). A continuum of disease exists for patients with ZES.[18,36] As Table 9 depicts, patients with hepatic metastases fare poorly, followed by patients with metastatic nodal disease. Patients with an identified primary or patients without identifiable disease fare best. No patient who underwent excision of nodal disease without a demonstrable primary tumor was "cured."

Tumor location is important prognostically. Reports[54,55] have shown that patients with extrapancreatic gastrinomas have longer survival. In our study, patients with primary duodenal tumors fared best (Fig. 2) because of their increased likelihood of resectability (including six "cures").

TABLE 9. *Survival Based on Pathologic Findings Encountered*

	n	Average Survival (yr)	Died of Tumor No. (%)
No identifiable tumor	24	13.7	1/4 (25)
Primary disease only	32	10.2	5/14 (36)
Nodal metastases	14	7.0	6/7 (86)
Hepatic metastases	20	5.4	12/14 (86)
	90	9.6	24/39 (62)

Some authors have not found gastrinoma size to be a significant predictor of survival.[54] The prognostic significance of tumor size in this study again points to ZES being a continuum of disease. The longer the duration of tumor burden, the larger the lesion and subsequent shorter survival time from diagnosis (Fig. 3).

Improved survival among MEN-I patients is controversial. Multiple reports show a survival advantage for ZES patients with the MEN-I variety.[4,50] We and others[56] found no significant difference in long-term survival.

Conclusion

Although complete resection of tumor burden occurs in a minority of patients with ZES, surgical exploration should be the initial treatment in most patients without liver metastases, because it remains the only chance for "cure." Pharmacologic therapy is highly effective and should be the principle treatment for patients who are not surgically cured. Prognostic factors correlating significantly with long-term survival are small tumor size, absence of metastatic disease, and a nonpancreatic location of the primary tumor.

Future efforts should be devoted to improved preoperative tumor localization, increased emphasis of the importance of duodenal micro-gastrinoma, and a cautiously aggressive surgical approach to the ZES patient with MEN-I.

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DISCUSSION

DR. JAMES C. THOMPSON (Galveston, Texas): When I was a senior medical student in Galveston, we had a dermatologist whose lifelong interest was in a rare disease, bullous pemphigus. He collected these people. When I was a senior, our hospital was full of these folks; I was scared to death I was going to get bullous pemphigus. I have not seen a patient with the disease since. It is funny how we get preoccupied with rare diseases.

The Zollinger-Ellison syndrome is not exactly a great epidemiologic threat. Many normal people, surgeons, go through a lifetime and never see one of these patients. And yet you can see how we have been fascinated by them. I will bet it has been talked about in the literature more than a lot of really common, important diseases because they are so dull. Well, this disease is not dull. I mean, anytime you read about it, it changes. It is remarkable, in fact, that everybody who treats it seems to have a different idea about how it ought to be treated right now.

One of the things I am really interested in is the idea that it is an experiment in nature. I hate that phrase, but it is absolutely correct. We had a woman who was 72 years old and came in to see us with diarrhea. We got an upper GI series because I did not know what else to do, and she had these great redundant mucosal folds. And our radiologist said she probably had this Zollinger-Ellison syndrome. This was 1970, and I was floored by that suggestion. We measured her gastric acid, and she made 55 mEq basal acid per hour—55 mEq! And she did not have a duodenal ulcer; she did not have an ulcer anywhere. Just think about that! She must have had some kind of ironclad duodenum. She also had a thousand picograms of gastrin per milliliter. And we operated on her, did a total gastrectomy, and she really did fine.

I think we ought to recognize that there have been several phases of surgical interest in this disease. First of all, we were preoccupied with the potential lethal consequences of the hypersecretion of acid, and at that time we directed our interests to a total gastrectomy. Then after the H_2-blockers came along, there was a period of absolute nihilism, which was championed by a fellow named Dennis McCarthy, who stated that these patients should not be operated upon. Then, thirdly, there was a gradual realization that these folks tend to die of their tumors, and there were several National Institutes of Health papers with Bob Jensen and Jerry Gardner, documenting the poor tumor responses to chemotherapy. And then synchronous with that was a period in which we realized that we ought to treat these patients surgically, aiming at preventing death of cancer, which is what a malignant gastrinoma is—it is cancer. And we owe Ed Pasarro at the VA Hospital in Los Angeles a tremendous debt, because he has shown us that these tumors are actually findable and that most of them can be eradicated. His last 10 years, they have had a 58% incident of eugastrinemia, that is, normal gastrin levels, after operating on these people, finding the tumors, and removing the tumors.

Now this paper reports that only 11% of their patients achieved eugastrinemia, which I am embarrassed to say is about what we have. Most recent papers report greater than 50%, and I would like to ask the authors, what has been their recent experience? That is, have you been able to find and resect these duodenal microgastrinomas that have been recently reported and brooded about everywhere? What has been the fate, as far as living, of your multiple endocrine neoplasia (MEN) patients? We, like you, have never been able to render a single one of them eugastrinemic for more than 4 months. Now there is a trick here, and that is you operate on some of them, take out a whole lot of their gastrin-producing tissue, and they will be eugastrinemic for a while and you will be going around smiling. But then a lot of them, in fact, every one of the MEN patients in our experience, ultimately achieve the ability of their metastases to secrete gastrin. What has surprised us is that of our 11 MEN patients, only one has died, and that patient came in to us with massive hepatic metastases. We have 10 of them living with high levels of gastrin, some of them more than 2000 pg/mL. They appear to be impossible to cure but quite resistant to death. I do not understand that. And what has been your death rate, is what I would like to know, at the Mayo Clinic?

And, lastly, I would like to say that I do not know that a Whipple is ever justified in this operation. Some people are doing them, but I think that it is really hard to justify. And what has been your (1) cure rate with a Whipple, and (2) mortality rate in the four patients that you did do it on?

And, lastly, you reported a 4% mortality rate, and I would just like to know how those folks died. Thank you very much.

DR. ROBERT ZEPPA (Miami, Florida): Dr. Bland, Dr. Jones, Gentlemen, I rise only to ask a couple of questions of John after this elegant presentation. If I missed it, I apologize, but I thought I saw 150 patients, 90 of whom were treated surgically. What happened to the other 60? How have they fared and how were they treated? Thank you.

DR. WALLACE P. RITCHIE, JR. (Philadelphia, Pennsylvania): I certainly enjoyed the paper, and I completely agree with the conclusion that better methods of localization are needed.

John, have you had any experience selective intra-arterial infusion while measuring intraportal gastrin levels to see if you can localize tumors somewhere in the pancreas? We have done a few of these and are encouraged by it. I think that is something that needs to be explored further. I would be interested to know what your experience has been.

DR. DAVID FARLEY (Closing discussion): We would like to thank each of the discussants for their comments and pertinent questions. In particular, I appreciate Dr. Thompson's careful scrutiny of our study as well as his experienced thoughts on the Zollinger–Ellison syndrome.

In answer to Dr. Thompson's questions, our recent experience has proven more successful than our retrospective analysis shows to date. Within the past couple of months, we have identified several tumors in the duodenum and, fortunately, those patients are currently eugastrinemic, so we are encouraged. Secondly, our experience with the multiple endocrine neoplasia (MEN) patients has been significant. Approximately 33 patients in this retrospective study has the MEN-1 variant of gastrinoma. In the patients that we operated on, survival was no different than in the patients with sporadic type disease. But, again, this study has all the inherent problems of a retrospective analysis. Many of the patients who were not operated on were basically asymptomatic on medication, and they did extremely well and deferred surgery. Therefore, it is difficult to make comparisons, but at present, our operative experience has shown that there is no difference in our study between sporadic and MEN-1 variants.

We performed radical pancreatic duodenectomy on four patients. One of the four patients currently is eugastrinemic. We had a 0% operative mortality rate with that procedure. The four deaths that we noted in our study resulted from sepsis, myocardial infarction, gastrointestinal bleeding, and pneumonia. In answer to Dr. Zeppa's question, we did look at a total of 156 patients. Therefore, 66 of the patients were not treated surgically. Thirty-three of these patients had diffuse hepatic metastases as noted by abdominal computed tomography. Twenty of the patients deferred surgical management. These patients obviously had the Zollinger–Ellison syndrome, but the medication rendered them asymptomatic, and it was difficult to talk these patients into operative treatment when they felt perfectly fine on medication. Nine patients over the past 33 years had the MEN-1 variant with diffuse pancreatic disease; and at the time of this study, we did not believe that it was proper to operate on these people. This would not be our intention today. Two other patients were described as poor anesthetic risks and were refused operative treatment. The selected arterial secretin injection (SASI) test is a very new test devised by the Japanese, and they have had success with regionalizing gastrinomas. But we, however, think, as Dr. Pasarro has shown, that basically 90% of all tumors are located within the gastrinoma triangle and, therefore, we do not believe that this test offers us a great benefit.

In summary, although recent reports are encouraging for the surgical treatment of localized sporadic-type gastrinomas, we remain disappointed in the modern-day ability to localize all tumors and, more specifically, to treat those patients with MEN-1 variant of Zollinger–Ellison syndrome. There is, however, reason for optimism on both fronts. Recently, a group of European investigators accurately localized gastrinomas in 10 patients using indium-labeled pentatreotide. This modified somatostatin analog was given intravenously, and detailed localization via nuclear imaging was evident in all 10 patients at 24 hours. Although this is a small study, we may be entering a new era of improved preoperative tumor localization.

Although we did not render any of our patients with the MEN-1 variant of Zollinger–Ellison syndrome eugastrinemic, two separate groups have recently reported encouraging results within the past year. Dr. Norman Thompson's group from the University of Michigan and Dr. Pipeleers-Marichal and colleagues from France have each had success rendering patients eugastrinemic with the MEN-1 variant of Zollinger–Ellison syndrome. Both groups advocate resection of obvious gastrinoma as well as lymph node dissection along the duodenum and up into the hepatoduodenal ligament as well as a standard distal pancreatectomy. But, most importantly, they encourage us to evaluate the duodenum thoroughly and remove any palpably abnormal tissue. This is done through a longitudinal duodenotomy. The optimism of these reports must be tempered, however, in that only a few of these patients actually have normal secretin-stimulated gastrin values after operation. Although follow-up is short, this aggressive technique has yielded encouraging results and certainly warrants further consideration. Thank you very much.

Percutaneous Catheter Drainage Compared With Internal Drainage in the Management of Pancreatic Pseudocyst

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The records of 92 patients with symptomatic pancreatic pseudocysts referred for surgical management over a 27-year period were retrospectively reviewed to compare outcome in 42 patients managed with operative internal drainage procedures (group I) with that in 52 patients managed with computed tomography–directed percutaneous catheter drainage (PCD) (group II). The two groups were similar for patient age, sex, pseudocyst location, and cause. The frequency of antecedent pseudocyst-associated complications was less in group I (16.7 *versus* 38.5%, $p < 0.05$). Seven group I patients and four group II patients had major complications (16.7 *versus* 7.7%, not significant). Group II mean duration of catheter drainage was 42.1 days, and the drain track infection rate was 48.1%. The frequency of antecedent operative cyst drainage was similar (14.2 *versus* 13.5%), as was the frequency of subsequent operations for complications related to chronic pancreatitis (9.5 *versus* 19.2%, not significant). Mortality rate was greater in group I (7.1% *versus* 0%, $p < 0.05$). Pseudocysts can be effectively managed either by open operation with internal drainage or by PCD. Drawbacks of PCD include the controlled external pancreatic fistula and the risk of drain track infection. Percutaneous catheter drainage has the following advantages: (1) low mortality rate, (2) does not require a major operation, (3) does not violate the operative field in cases when subsequent retrograde duct drainage procedures are required. Neither PCD nor internal drainage is definitive, and with either technique subsequent correction of underlying pancreatic pathology may be necessary.

PERCUTANEOUS CATHETER DRAINAGE (PCD) of pancreatic pseudocysts with computed tomography (CT), ultrasound, and fluoroscopic guidance has been increasingly employed as an alternative or adjunct to operative drainage of pancreatic pseudocysts over the past decade.[1-3] Over the years, the cornerstone of therapy for symptomatic pancreatic pseudocysts has been internal drainage with cystgastrostomy, cystduodenostomy, or cystjejunostomy.[4-6] To evaluate the role of percutaneous catheter drainage in the management of pancreatic pseudocysts, we compared the clinical presentation and outcome in patients managed with operative internal drainage with that in those managed with CT-directed PCD over a 27-year period.

Subjects and Methods

The records of 42 patients with symptomatic pancreatic pseudocysts who were managed with operative internal drainage from 1965 to 1991 (group I) and 52 patients treated with PCD from 1982 to 1991 (group II) were reviewed retrospectively. Patient age, sex, pseudocyst cause, cyst location, antecedent pseudocyst-related complications, procedures performed in the management of pseudocysts before referral, procedures employed in management, postoperative morbidity and mortality rates, and length of hospital stay were analyzed.

Operative or radiologic intervention was undertaken electively; patients with severe acute pancreatitis, infected pancreatic pseudocysts, and pancreatic abscess were excluded. Selection of cystgastrostomy, cystduodenostomy, or cystjejunostomy was based on cyst location. Initially, we employed PCD to treat patients with major medical comorbidity; subsequent experience with this technique has increased over the study period (Fig. 1). Percutaneous catheter drainage currently is used almost exclusively to treat symptomatic pancreatic pseudocysts larger than 5 cm in diameter without evidence of associated pancreatic duct dilation on CT scan. Percutaneous catheter drainage was performed in the radiology department under local anesthesia with CT guidance. Needle and guide wire localization preceded placement of a 7- to 12-French pigtail catheter into the collection, which was connected to a

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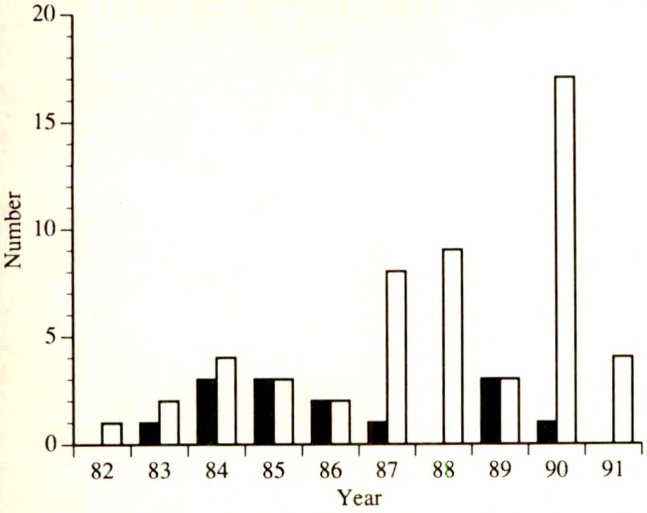

FIG. 1. Percutaneous catheter drainage has been used increasingly since it was first introduced in 1982. ■, internal; □, percutaneous catheter drainage.

closed drainage system (Fig. 2). Bacterial and fungal cultures of the fluid were obtained initially and were repeated when patients developed fever or leukocytosis. Discrete variables in group I and group II were compared with the chi square tests. Continuous variables were analyzed with Wilcoxon's rank sum tests. Significance was accepted when $p < 0.05$.

Results

The two groups were similar for age, sex, pseudocyst location, and underlying cause (Table 1). Most pseudocysts represented complications of pancreatitis due to alcohol abuse. Other causes of pseudocysts included biliary pancreatitis, operative or blunt trauma, and sarcoidosis. Four patients in group I and three in group II had more than one cause or were classified as having idiopathic pancreatitis. Multiple cysts were present in three patients in group I and two patients in group II.

Pseudocyst-related complications present at the time of treatment were seen more frequently in group II (Table 2). Cyst-enteric fistulas were less frequent in group II; however, pancreatic ascites, pancreatopleural fistula, biliary obstruction, duodenal obstruction, and splenic vein occlusion were more common.

Antecedent cyst drainage procedures were noted with similar frequency in both groups (Table 3). One patient in group II had undergone PCD 1 year previously.

Twenty-seven patients in group I were managed with cystgastrostomy, nine with cystduodenostomy, and six with cystjejunostomy. Three patients in group I had multiple cysts; one had a double cystgastrostomy and two were managed with cystgastrostomy and caudal pancreatectomy with cyst excision. In group II, both patients with multiple cysts were managed with two percutaneous catheters.

Treatment morbidity rate is summarized in Table 4. Seven patients in group I and four patients in group II had major complications, including hemorrhage, sepsis, respiratory failure, and myocardial infarction (16.7% *versus* 7.7%, not significant). In group II, mean duration of catheter drainage was 42.1 days (range, 6 to 210 days). Twenty-five of 52 patients (48.1%) developed drain track infections; organisms cultured from drainage fluid are listed in Table 5. In 11 patients cultures yielded single organisms. Staphylococcal species were frequently cultured, present in 22 of 25 (88.0%) of patients. The duration of drainage was less in patients with negative cultures

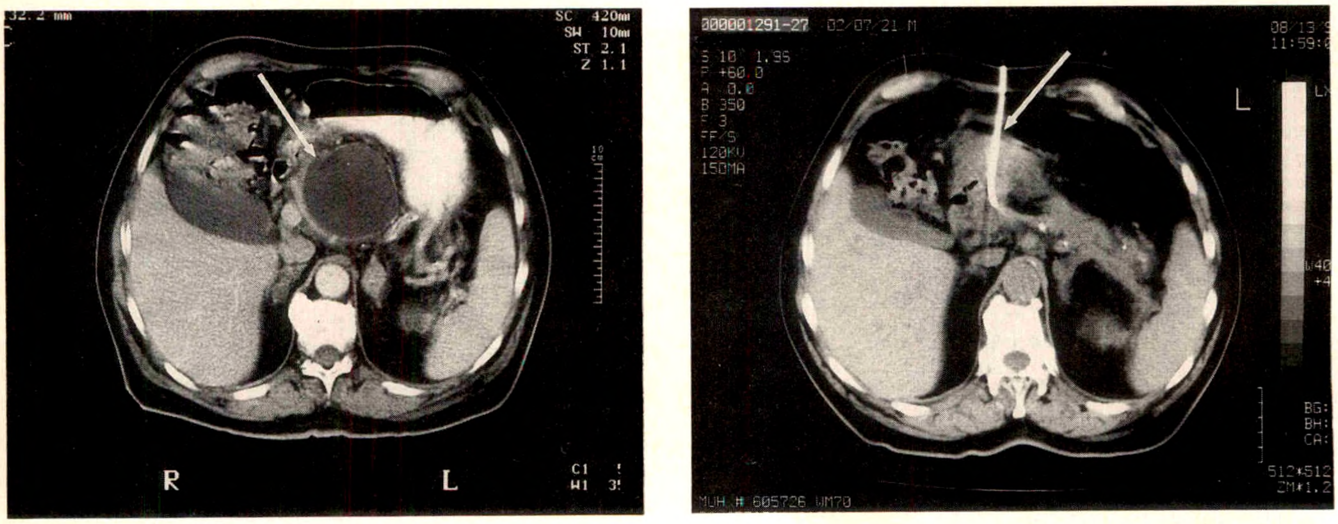

FIG. 2. (A, left) Computed tomography scan showing pseudocyst in region of pancreatic head (white arrow). (B, right) Five days later, needle and guidewire localization preceded placement of 8-French pigtail catheter (white arrow) into cyst.

TABLE 1. *Patient, Sex, Age, Pseudocyst, Cause, and Predominant Cyst Location*

	Group I (Internal) n = 42	Group II (Percutaneous Catheter Drainage) n = 52
Sex		
M	29 (69.0%)	44 (84.6%)
F	13 (31.0%)	8 (15.4%)
Age (yr)		
Mean	45.5	43.2
Range	23–72	21–66
Pseudocyst cause		
Alcohol abuse	31 (73.8%)	42 (80.8%)
Gallstones	5 (11.9%)	3 (5.8%)
Other	6 (14.3%)	7 (13.5%)
Pseudocyst location		
Head	12 (28.6%)	13 (25.0%)
Body	23 (54.8%)	29 (55.8%)
Tail	7 (16.7%)	10 (19.2%)

(mean, 24.2 *versus* 61.4 days; median, 18 *versus* 55 days, $p < 0.05$). Organisms cultured from drainage were not present in concomitant blood cultures obtained from 16 patients. Length of hospital stay was similar (mean, 36.7 *versus* 39.8 days; median, 36 *versus* 30 days, not significant).

There were three postoperative deaths in group I (Table 6) and none in group II (7.1 *versus* 0%; $p < 0.05$).

Subsequent operations required for complications related to chronic pancreatitis are listed in Table 7. In group I, four patients had subsequent operations. One patient who had a cystjejunostomy developed chronic pain in association with a dilated pancreatic duct, which was managed with lateral pancreaticojejunostomy 1 year later. Two patients required gastrojejunostomy for gastric outlet obstruction due to duodenal stenosis, and one required a biliary enteric bypass. In group II, two patients subsequently underwent lateral pancreaticojejunostomy, one in combination with biliary enteric bypass. Three patients had nondilated pancreatic ducts with strictures in the genu or midbody; two had retrograde drainage of the duct after caudal resection using a caudal pancreaticojejunostomy. The third had a resection of a cyst and midbody stricture with pancreatic duct ligation. Another patient developed ductal obstruction in the tail of the pancreas after splenectomy for traumatic splenic rupture with prolonged pseudocyst drainage, which was managed with caudal resection and caudal pancreaticojejunostomy. Two patients had subsequent vagotomy and gastrojejunostomy for gastric outlet obstruction due to duodenal stenosis. Two patients with multiple cysts initially treated with PCD had retrogastric collections, which were inaccessible to PCD and required operative external drainage.

TABLE 2. *Antecedent Complications*

	Group I (Internal) n = 42	Group II (Percutaneous Catheter Drainage) n = 52
Cystenteric fistula	4	1
Pancreatic ascites	1	10
Pancreatopleural fistula	0	3
Biliary obstruction	1	4
Duodenal obstruction	0	2
Splenic vein occlusion	1	3
Total patients*	7 (16.7%)†	20 (38.5%)

* Includes patients with multiple complications.
† $p < 0.05$ compared with Group II.

TABLE 3. *Antecedent Cyst Drainage Procedures*

	Group I (Internal) n = 42	Group II (Percutaneous Catheter Drainage) n = 52
Cystgastrostomy	4	4
Cystjejunostomy	1	0
External drainage	1	2
Percutaneous catheter drainage	0	1
Total patients	6 (14.2%)	7 (13.5%)

Discussion

The two groups were remarkably similar in terms of patient characteristics such as age, sex, and pseudocyst location and number. The underlying cause was predominantly chronic pancreatitis secondary to alcohol abuse, consistent with previous reports in the literature.[4-11]

Both groups contained examples of pseudocyst complications that were present at the time treatment was initiated. The number of antecedent complications was substantially higher in group II. This was, at least in part, related to improved diagnostic technology available in the later years of the review, and accounts for an increased frequency of identification of pancreatic ascites (CT), biliary stricture (endoscopic retrograde cholangiopancreatography), and splenic venous occlusion (CT, splanchnic angiography).[12]

TABLE 4. *Morbidity*

	Group I (Internal) n = 42	Group II (Percutaneous Catheter Drainage) n = 52
Hemorrhage	2 (4.8%)	1 (1.9%)
Sepsis	2 (4.8%)	1 (1.9%)
Respiratory failure/pneumonia	2 (4.8%)	1 (1.9%)
Myocardial infarction	1 (2.4%)	1 (1.9%)
Gastric ileus	1 (2.4%)	0
Colonic ileus	0	1 (1.9%)
Pneumothorax	0	1 (1.9%)
Pancreatocolonic fistula	0	1 (1.9%)
Dislodged catheter	0	3 (5.7%)
Drain track infection	0	26 (50.0%)
Pancreatocutaneous fistula	0	52 (100%)

TABLE 5. *Organisms Cultured From Drainage Catheters in 25 Patients*

Organism	Patients (n)
Gram-positive organisms	
Coagulase-negative Staphylococcus	13
Staphylococcus aureus	8
Enterococcus sp.	4
Corynebacterium sp.	1
Methicillin-resistant *Staphylococcus aureus*	1
Streptococcus viridans	1
Streptococcus sanguis I	1
Gram-negative organisms	
Pseudomonas aeruginosa	5
Escherichia coli	3
Enterobacter cloacae	2
Proteus mirabilis	2
Pseudomonas maltophilia	2
Pseudomonas fluorescens	1
Klebsiella oxytocca	1
Klebsiella pneumoniae	1
Serratia marcescens	1
Acinetobacter calcoaceticus var. anitratus	1
Bacteroides ovatus	1
Fungal organisms	
Candida albicans	2

The complications resulting from internal drainage procedures differed, both in type and magnitude, from those associated with PCD. Major complications after internal drainage consisted of gastrointestinal hemorrhage, sepsis, respiratory failure and pneumonia, and myocardial infarction, and were similar to previous reports for this procedure[4–6,13]; the morbidity rate of 16.7% was consistent with recent reports of operative management of pancreatic pseudocysts.[8–10,14–16] Similar complications occurred in patients with PCD and, although less frequent, the difference was not significant. Previous experience with external pancreatic fistula after operative external drainage of pancreatic pseudocysts indicated that most fistulas close spontaneously over the course of 2 to 6 weeks.[17] Our results are similar to this experience. Octreotide acetate, a somatostatin analog, inhibits pancreatic exocrine secretion[18–20] and holds considerable promise for accelerating closure of pancreatic fistulas after PCD.

The most prominent problem encountered in the use of PCD was the high rate of drain track infection. All of these patients had clinical findings indicating infection, including fever or leukocytosis, which was treated with appropriate systemic antibiotics and responded promptly; none developed concomitant positive blood cultures or an abscess that required operative drainage. We presume that these infections were caused by skin contaminants, based on the high number of infections caused by resident normal flora of the skin. Also noted were a high number of infections with gram-negative bacilli, organisms known to colonize the skin of hospitalized patients.[21] The insertion of catheters through the skin may lead to local infection, which can progress to deep infection and bacteremia. A direct relationship has been observed between duration of catheterization and the incidence of infection with indwelling intravascular catheters.[22] Our findings were similar with PCD; drain track infection was associated with increased duration of catheter drainage. The obvious importance of drain track infection and its effect on the length of fistula drainage dictates a need to improve the technique of catheter management during PCD. During the period of study, sterile dressings were maintained over the catheter site at skin level. We have established a catheter care protocol similar to that employed with central venous lines in an effort to reduce the rate of drain track infection. Antiseptic and antibiotic catheter irrigations have not been employed.

Three deaths occurred in the group I patients (7%); this is consistent with recent studies of internal drainage, which reported mortality rates ranging from 8% to 13%.[4–7,13] The three deaths occurred in the middle decade of the study; sepsis and associated respiratory failure were major factors. Whether modalities of treatment currently available, including advances in anesthesia, improved antibiotic therapy, and better respiratory therapy would have prevented these unsatisfactory outcomes is problematic.

TABLE 6. *Postoperative Deaths in Group I*

Year	Age	Sex	Operation	Comorbid Conditions	Complications	Postoperative Day of Death
1972	72	F	Cystgastrostomy, cholecystectomy, common bile duct exploration, cholangiogram excision cystjejunal fistula	Cholelithiasis, cystjejunal fistula	Staphylococcal sepsis, upper gastrointestinal bleeding due to gastritis, myocardial infarction	76
1978	40	M	Cystgastrostomy	Head and neck squamous cell cancer	Gram-negative sepsis, adult respiratory distress syndrome	16
1979	24	F	Cystgastrostomy	None	Pneumonia, adult respiratory distress syndrome	42

TABLE 7. *Time Interval From Drainage Procedure to Subsequent Operation for Management of Chronic Pancreatitis*

Operation	Group I (Internal) n = 42 No. (Interval)	Group II (Percutaneous Catheter Drainage) n = 52 No. (Interval)
Lateral pancreaticojejunostomy	1 (1 yr)	2 (1 yr)
Caudal pancreaticojejunostomy	0	3 (<1 yr)
Caudal pancreatectomy with cyst excision	0	1 (<1 yr)
Gastrojejunostomy	2 (2 yr, 1 yr)	2 (<1 yr)
Biliary–enteric bypass	1 (4 yr)	1 (1 yr)*
External cyst drainage	0	2 (<1 yr)
Total patients	4 (9.5%)	10 (19.2%)

* Also had lateral pancreaticojejunostomy.

No deaths have occurred up to the present in patients treated with PCD.

The length of hospital stay was similar in the two groups. In group I, timing of the internal drainage procedure often was determined by a policy to perform the operation approximately 6 weeks after the cyst became clinically apparent. This was based on evidence that some pseudocysts spontaneously resolve during this interval,[23] and that cysts that persist develop a dense fibrous wall that facilitates a safe cystenterostomy. After operation, the recovery period for internal drainage was usually short in uncomplicated cases. In group II patients, less importance was attached to the development of cyst wall maturity, and catheter drainage was instituted soon after diagnosis of the pseudocyst. Much of the hospitalization was required to stabilize and manage the resulting external pancreatic fistula and associated drain track infections. Although several early reports suggested that fistulas that occur after PCD close over the course of several weeks,[1-3] our mean drainage time was 6 weeks.

It is important to emphasize that successful elimination of a pseudocyst by any means cannot be expected to correct the underlying chronic pancreatitis that is responsible for the development of the pseudocyst in most cases. A number of patients in both groups required previous pseudocyst drainage, and therefore represented a recurrence of the problem. Not unexpectedly, a similar number of patients treated either with internal drainage or PCD subsequently have required surgical procedures to manage progression of the underlying pancreatitis. This fact supports the logic of combining a retrograde drainage procedure and cyst decompression or resection whenever possible. For example, smaller cysts often can be decompressed and incorporated into a lateral pancreaticojejunostomy to achieve a more definitive correction both for the pseudocyst and the underlying obstructed and dilated pancreatic ducts. Smaller cysts located in the pancreatic tail can be resected and the pancreatic duct drained either with caudal or lateral pancreaticojejunostomy.

Rarely, pancreatic neoplasms may present as pseudocysts. We are aware of two patients with pancreatic ductal adenocarcinoma who presented with a pseudocyst that developed secondary to ductal obstruction during the study period. These patients were managed initially with internal drainage only to return with evidence of tumor progression; accordingly, they were excluded from the study. Warshaw et al.[24] have emphasized that tumors may masquerade as pseudocysts; this is particularly true with rare cystic neoplasms such as pseudomucinous cystadenocarcinoma. This uncommon occurrence provides justification for biopsy of the cyst wall at the time of internal drainage to avoid overlooking a neoplastic process. It also raises a modest level of concern in cases in which PCD is employed. Failure of cyst resolution, early reaccumulation of a cystic collection, or persistence of the cyst wall should raise suspicion that a tumor, rather than a simple pseudocyst, may be present. To our knowledge, we have not encountered this problem in any patient managed with PCD.

Several recent reports emphasize that asymptomatic or minimally symptomatic pancreatic pseudocysts identified on CT scan can be safely managed nonoperatively.[25,26] This experience indicates that about one half to two thirds of patients managed expectantly will avoid operation over an observation period longer than 1 year. Multiloculated cysts and cysts larger than 6 cm in diameter were more likely to require operative treatment.

Our findings indicate that pancreatic pseudocysts can be successfully managed with either operative internal drainage or percutaneous catheter drainage. Internal drainage requires a period of observation before operation to permit maturation of the cyst wall; however, the postoperative recovery usually is prompt, and postoperative pancreatic fistula is rare. Complications occur in approximately 20%, with sepsis a major factor. Current mortality rates are below 6%.[8,9,16,25,27] Percutaneous catheter drainage can be instituted early in the course, and has the obvious advantage of avoiding a major abdominal operation, which violates the surgical field in those cases requiring a subsequent procedure such as lateral pancreaticojejunostomy to correct underlying pancreatic ductal obstruction associated with chronic pancreatitis. The principal disadvantage of PCD is the resulting pancreatic fistula, which in our experience required 6 weeks to close, and which carried a substantial risk of infection; the latter problem responds to antibiotic therapy, but is associated with an extended drainage period. We have not encountered a death that occurred as a consequence of PCD when employed electively in the management of pseudocysts.

In considering the approach to pancreatic pseudocysts, the size as well as associated pancreatic pathology enter into the choice of management:

Asymptomatic pseudocysts less than 6 cm in diameter often can be followed with an expectation of complete resolution in most cases and with a low incidence of complications.

Small symptomatic pseudocysts that occur in association with a dilated pancreatic duct can be decompressed and incorporated into a lateral pancreaticojejunostomy used for ductal drainage.[28] Occasionally, smaller cysts in the tail may be associated with little or no ductal dilation. Because of their location, they are difficult to drain internally or externally and carry a risk of hemorrhage because of the close proximity to the spleen and its pedicle. We have resected these, along with the spleen, and drained the transected pancreas with a caudal pancreaticojejunostomy with success.

Because of their location, large pseudocysts preclude any definitive approach to the underlying pancreatic inflammatory disease, and our management preference is PCD. This approach should be undertaken recognizing that subsequent operative correction of underlying pancreatic pathology may be required. We continue to use internal drainage when PCD is not possible because of pseudocyst location.

The principal disadvantages related to PCD include prolonged external pancreatic fistula and secondary infection of the catheter track. Both of these problems may be in part correctable using somatostatin analogs to promote early fistula closure and fastidious attention to the prevention of drain track infections.

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DISCUSSION

DR. GEORGE JORDAN (Houston, Texas): Dr. Bland, Dr. Jones; Drs. Anderson and Adams very kindly sent me a copy of their manuscript, and I recommend careful reading of this manuscript to all of you because it contains a lot of information that Dr. Anderson did not have time to present in his report today. The initial treatment of pseudocyst was primarily by external drainage. And as all of you know, a number of techniques were developed. This included marsupialization, which is a highly morbid procedure, really. Most commonly, the external drainage was by catheter drainage. The problem with external drainage in those days was the fact that everyone developed a pancreatic fistula, as was true in this series, and, secondly, there was a 20% incidence of recurrence of the pseudocyst; the development of internal drainage tended to prevent both of those late problems.

There are a number of items to note in this report. One is the tremendous increase in pancreatic pseudocysts that have been treated by Dr. Anderson and Dr. Adams in recent years. It took them 27 years to get 42 internal drainage procedures and only 8 years or so to get 52 radiographic catheter drainages. I am curious as to whether there has truly been an increased incidence of this problem or whether there is interest in putting catheters in, in circumstances where we would not have subjected the patient to an operation for drainage. The problem, obviously, with catheter drainage has been primarily the development of the fistula. And in the substance of the paper, it is pointed out that the chronicity of the fistula after this procedure has been much greater than anticipated.

Dr. Anderson did not discuss the handling of the catheter, and I would ask him to do that in his closing remarks. These are pigtail catheters, and I have always believed that once a fistula has developed that the drainage tube or catheter should be moved away from the pancreas. It should not be totally removed because the skin may close prematurely, but it should be moved away from the pancreas because I firmly believe that a catheter remaining in contact with a fistula prevents fibrous development and closure of the fistula.

The absence of mortality is certainly impressive and, it is hoped that will continue. In the management of the chronic fistulas, they apparently have only recently started using somatostatin and its analogs. Our own experience has been limited with it. As you know, there are those who feel that this is the answer to pancreatic fistulas. I have not found it to be so. Some people seem to respond; other people just do not seem to have any change in the course of their disease. Dr. Anderson did not mention the use of endoscopic retrograde cholangiopancreatography or sinograms in the management of these patients, and in our experience there are many patients with whom these tests are helpful, both in defining pathology and in directing surgical treatment, as well as in evaluating the possible cause of the prolonged drainage when a fistula occurs. As was true in his experience and has been in ours, the fistulas do close, but some of them do stay open for a long time. Surgical repair, however, is virtually never required. Thank you.

DR. ROBERT HERMANN (Cleveland, Ohio): Dr. Bland, Dr. Jones, Members and Guests, I would like to congratulate Dr. Anderson and Dr. Adams for this excellent review and comparison study of pseudocyst management. The manuscript is rich in detail, as Dr. Jordan mentioned, and I appreciate the opportunity to have reviewed it for this discussion. The principal message of the report, I believe, is that percutaneous catheter drainage with computed tomography guidance is safe and is equally effective as open- operative drainage in this group of patients.

Although the two groups were similar in almost all parameters, it must be re-emphasized that group 1 patients were treated over a 26-year period whereas group 2 patients were treated only during the past 9 years. This difference in time periods with the many differences in diagnostic and therapeutic modalities that were introduced during that time could well account for the differences in morbidity and mortality rates between the two groups. Furthermore, I think it is important to recognize that all patients were treated electively, and excluded from the study were patients with acute pancreatitis and patients with infected pseudocysts or abscesses. It is important to recognize that this is a selective group of patients, predominantly patients who develop pseudocysts from chronic pancreatitis, although the authors did not identify how many patients in either group had pseudocysts as a result of acute pancreatitis.

Finally, the size of the pseudocyst is an important criteria. The authors state that currently percutaneous catheter drainage is used almost exclusively to treat symptomatic pseudocysts larger than 5 cm in diameter without evidence of pancreatic duct dilatation on computed tomography scans. I have two questions for the authors: First, how many patients in this series had a pseudocyst after an episode of acute pancreatitis, and would you treat this patient with percutaneous catheter drainage as well as the group of patients with chronic pancreatitis? And, secondly, in the patient with chronic pancreatitis who develops a large pseudocyst 5 or 6 cm in diameter but has obstructive changes in the pancreatic duct as seen on an endoscopic retrograde cholangiopancreatogram, would you use catheter drainage as a first approach or as part of a staged approach to the problem? Or just go on with an operative internal drainage as definitive treatment? I enjoyed the paper very much, and I recommend it to you for your reading. Thank you.

DR. WILLIAM NEALON (Galveston, Texas): Dr. Bland, Dr. Jones, Members and Guests, I also would like to congratulate the authors on a superb presentation of their retrospective study of 92 patients treated for pseudocysts of the pancreas. As Dr. Jordan mentioned, a well-documented problem with external drainage that surgeons looked at long ago was the high rates of recurrence and pancreatic fistula that resulted. Percutaneous computed tomography directed drainage behavior in a similar manner, and recurrence rates have been quite high. The way to try to reduce those recurrence rates was to leave the catheter in for long periods. The resulting complication with long-term external drainage was a higher rate of infection. Dr. Anderson states that 25 of his patients who were externally drained had infection of the tract, which he distinguishes from sepsis on the basis of an absence of positive blood cultures. I wonder if Dr. Anderson would mind giving us a few more details about the patients with the so-called tract infection and whether any of them actually looked acutely ill.

I notice that ten of the patients who had external drainage had a finding of pancreatic ascites. It has been our experience that with pancreatic ascites, endoscopic retrograde cholangiopancreatogram (ERCP) defines a communication between the pancreatic duct and the peritoneum. We consider these patients poor candidates for external drainage because of the likelihood of continued drainage of the duct and fistula. I wonder if you have any information on your ascites patients, whether they have fared any better or worse than your long-term results overall.

You do not mention any recurrence in the percutaneously drained patients, and I do not know if that means that you had 0% recurrence after the drainage or not. Can you tell us what your information is on recurrence? Obviously, one of the down sides of percutaneous drainage is the fact that you may prolong the hospitalization, and your mean hospitalization of 42 days for your patients who were drained is testament to that fact. I was surprised to see the length of hospitalization for your operatively drained patients, and I wonder if you could give us some information on the reason for those prolonged hospitalizations.

Finally, approximately 4 years ago, I presented to this society some information on prospectively evaluating ERCP information in patients with pseudocysts. As Dr. Hermann mentioned, these could be very valuable in making a strategy, specifically in unanticipated patients with chronic pancreatitis. I wonder if you have any information on ERCP evaluation of these patients. Specifically, were any of the patients treated with a combined Puestow as well as pseudocyst drainage when you had that kind of information before operation? I thank the Society for the privilege of the floor.

DR. J. LYNWOOD HERRINGTON, JR. (Nashville, Tennessee): Dr. Bland, Dr. Jones, Members and Guests, I really have enjoyed this presentation very much, and I would like to congratulate Andy on his experience with percutaneous catheter drainage. I have had the opportunity recently to review numerous papers on the management of pancreatic pseudocysts for a surgical modality that Andy Warshaw and I recently put together. I think the results shared this morning are really superb. They are simply outstanding. There are, however, many groups around the country and abroad who cannot report such excellent results with percutaneous drainage because it is associated with significant complications and not infrequently it does not get the job done. I do think that we should not, by any means, give up internal drainage of the pancreatic pseudocyst because it is an excellent operation with few complications and good long-term cure rates. I would give consideration, however, to performing percutaneous catheter drainage as the initial procedure for the high-risk patient with a symptomatic pseudocyst. As you know, endoscopy-guided catheter drainage has been recently reported with some success in a few centers, but very few clinics, relatively speaking, have had significant experience with this new modality.

Andy, I would like to ask you three questions: In performing a cyst gastrostomy do you ever drain the cyst cavity with a Penrose drain and bring it out through the anterior gastrotomy incision or closure? I know that some groups advocate that.

Also, some recent authors, particularly in Europe, have reported unsatisfactory results from internal drainage using cyst gastrostomy for huge cysts 10 to 15 cm or more in diameter, even when they present entirely behind the pancreas. I have had good results in my limited experience with huge cysts just using the pancreatic cyst gastrostomy and have used Roux-en-Y drainage only when the cyst presents up against the transverse mesocolon. Now, Andy, how would you manage a patient with an extensive enterocystic hemorrhage from a ruptured pseudoaneurysm of the splenic or the gastroduodenal artery, and what have your results been with this procedure? Again, I enjoyed the paper.

DR. DAVID ADAMS (Closing discussion): Thank you very much, Dr. Jones and Dr. Bland. Let me begin at the beginning with Dr. Jordan and comment on the incidence of pancreatic pseudocysts, which seem to have increased recently. Part of this is related to the fact that we have, in this study, excluded a number of patients who were treated with combined drainage procedures. If you look at the number of pseudocyst patients that Dr. Anderson has been involved with over the past 27 years, there were 160 patients. And so there are a number of patients who we have not identified in this study who were treated during the early study period when percutaneous cathether drainage (PCD) was not used. In addition, I think we will all agree that the use of computed tomography (CT) scans has changed the pattern of the presentation of patients with pancreatic pseudocysts.

The second question of Dr. Jordan's related to handling of the catheter. Dr. Anderson made allusion to the importance of the catheter care. I think in our earlier experience we have been frivolous in managing the skin care and dressing care with these catheters. Another important factor Dr. Jordan identified has to do with the proximity of the catheter to the pancreatic duct. And I think we would agree with him that proximity to the pancreatic duct increases the duration and the volume of the drainage. We have had several patients who have had catheters in the region of the head of the pancreas who, on sinogram studies, have demonstrated direct communication with the duct and the duodenum. These fistulas did not close until the catheter was withdrawn. Our experience with octreotide is limited also. We have reported five patients with prolonged pancreatic fistulas after PCD in whom octreotide has been used. These were patients with fistulas for longer than 4 weeks. We noted that there was diminishment after 24 hours to 52% in the fistula output and found that all these fistulas eventually closed. We currently are looking, in a prospective fashion in patients managed with PCD, randomizing them to treatment with octreotide and treatment without.

As for the question regarding the value of the endoscopic retrograde cholangiopancreatography (ERCP), currently our approach is to evaluate the duct from the back side. We use the ERCP in cases of recurrence of pseudocysts or associated complications, biliary obstruction, pancreatic ascites, or other problems. Sinograms are used routinely in the follow-up of the patients with PCD, and all patients who have PCD have either a weekly CT scan or a sinogram. The sinogram has been very important in assessing patients who have been what could be called failures of PCD, in that they required subsequent operations. The problem that has been most common that we have identified are patients who do not have a dilated pancreatic duct but have a localized stricture at the genu of the pancreas.

I appreciate Dr. Hermann's comments. Again, he made reference to the long time period of this study. I think we should be clear to emphasize in this discussion that we really are comparing apples and oranges. These are dissimilar groups of patients. There are, however, many similarities between apples and oranges. They are both round, both begin with a vowel, and both are fruits. And we have attempted to emphasize the similarities that we could between these two groups of patients. Dr. Herman asked about the number of patients who have had acute pseudocysts. We have been uncomfortable about classifying these patients as acute or chronic pseudocysts. We believe that most of these patients are chronic pseudocysts. We pay particular attention to the study that Dr. Nealon reported here several years ago, involving nine of 24 patients whom they had initially identified as having acute pseudocyst related to acute pancreatitis. On evaluation with ERCP, they found that they had changes of chronic pancreatitis. So we believe that in most of our patients, these represent chronic pancreatitis. And then again, Dr. Hermann mentioned the question of staging of pancreatic pseudocyst. That may be a euphemism for failed PCD, but I think we should embrace this term. In particular, we have found that patients who have biliary obstruction, who are malnourished, or who are unfit for a major operative procedure may benefit from PCD as a temporizing measure.

Dr. Nealon asked a very important question about infection *versus* colonization. And if you review this subject in the radiologic literature, they will make the point that infection is really not a problem; they have a lot of colonization, however. We have been unable to distinguish the difference in these two characteristics, in that all patients who grew organisms eventually developed fever or leukocytosis. This is a very important aspect of this treatment and will require further study. We have found in an initial group of 28 patients that we reported that the infection rate we identified was only 28%. With improved surveillance techniques, however, which involves weekly cultures, the infection rate is really fairly high.

The question of pancreatic ascites is of interest. What we have identified in this group of patients are localized cysts in the region of the head and body of the pancreas, which we have drained percutaneously. And, in many surprising instances, we have achieved resolution of the pseudocyst. It is interesting that one of our recurrences and perhaps a failure of PCD was a patient with pancreatic ascites who presented 1 year after his initial PCD with a dilated pancreatic duct, also associated with biliary obstruction. And at that time, this patient underwent a lateral pancreaticojejunostomy (LPJ) with cyst incorporation and a biliary enteric anastomosis. The recurrences after PCD can be looked at in a number of fashions. One, you can look at it as failure of PCD, in that patients require a drainage procedure immediately after removal of the catheter. The other is the group of patients who present subsequently, and there have been two patients who have presented more than 1 year later with recurrences of their pseudocysts. The question of the longevity of patients who have internal drainage, and their duration of hospitalization, may relate to historical factors and to the fact that we have kept many of these patients in the hospital a lot longer in the past than we do now, and we also worked under that dictum that a 6-week period of maturation was needed before cyst enterostomy. Again, regarding the question of the ERCP in the evaluation of the pseudocyst: we have been very comfortable in assessing duct diameter with the CT scan. And in a patient who has a dilated duct on CT scan with a moderate-sized pseudocyst, we embark initially on the LPJ with cyst incorporation and do not use PCD in those patients. And, finally, with Dr. Harrington's question related to the cyst gastrostomy, when those are performed we do not bring out a drain through the gastrotomy. A closed suction drain is laid in the region of the pancreatic bed and brought out through a separate incision. The problem with intracystic hemorrhage also was mentioned. Over the past 27 years, there have been 14 patients who have presented with intracystic hemorrhage. There has been one death in that group. We believe that the improvement in the mortality rate in this group of patients has been related to the use of selective mesenteric angiography in both the diagnosis and the management of these patients. Thank you very much.

The Use of UW Solution in Clinical Transplantation

A 4-year Experience

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The development of the University of Wisconsin (UW) cold storage solution has extended safe preservation of the liver and pancreas from 6 to 24 hours or more. From May 1987 until November 1991, 288 livers and 163 simultaneous pancreas/kidney transplants were performed using UW solution. The mean preservation times were: liver, 12.7 ± 4.4 hours, pancreas 17.2 ± 4.4 hours, and kidney, 19.2 ± 4.3 hours. Included in this series were 35 reduced-sized liver transplants, 7 cluster transplants, and 132 combined liver/pancreas retrievals. No differences in allograft function or graft-related complications were seen in organs preserved for less than or longer than 12 hours or in grafts from combined liver/pancreas retrievals. All pancreas/kidney transplants and most liver transplants were performed semi-electively. Actuarial 1-month patient and graft survival after liver transplantation was 91.4% and 80.2%, and at 4 years was 74.0% and 62.0%, respectively. After pancreas/kidney transplantation, the actuarial patient survival at 1 month and 4 years was 99.4% and 90.5%, respectively, whereas pancreatic and renal allograft survival at 1 month was 97.5% and 96.8%, and at 4 years was 83.0% and 83.4%, respectively. The ability to extend preservation times with UW solution has many advantages; however, the most important contribution of UW solution to clinical transplantation has been the increased utilization of scarce donor organs for more recipients because the previously imposed constraints on preservation time have been removed.

TWO METHODS OF kidney preservation were introduced in the late 1960s, one using continuous hypothermic pulsatile perfusion[1] and the other using simple cold storage.[2] Both methods have been used clinically for more than 20 years. These methods have allowed an increase in the number of kidneys available for transplantation and have made it possible to perform the transplant as a semi-elective procedure.

The introduction of cyclosporine into clinical transplantation in the early 1980s dramatically improved transplantation results for extrarenal organs such as the liver, pancreas, and heart, and more recently, for the lung. Methods that were successful for kidney preservation, however, were not of equal success for preservation of extrarenal organs. The limit of organ preservation was only 4 to 10 hours, which made organ sharing difficult and required extrarenal transplants to be performed on an emergency basis.

We presented our experimental results in 1986 at the American Society of Transplant Surgeons, using a canine model of pancreas preservation,[3] and demonstrated successful 72-hour preservation using the University of Wisconsin (UW) solution. A year later, at the International Transplant Conference in Pittsburgh, we showed that the liver could be safely preserved for 48 hours[4] and the kidney for 72 hours[5] with the same solution. Additionally, we presented our preliminary results using this solution for clinical liver preservation.

This report details our experience with the UW solution for organ preservation from its clinical introduction in 1987 until November 1991. During this period, we performed 288 liver transplants and 163 pancreas/kidney transplants, using the UW cold storage solution for preservation. Four hundred sixty-four cadaveric kidney transplants also were performed during the same period using continuous hypothermic pulsatile perfusion[6] but those data will not be presented in this article.

Materials and Methods

Liver Transplantation

A total of 288 liver transplants were performed between June 1987 and November 1991. Three hundred thirty-

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TABLE 1. *Indications for Primary Liver Transplantation in Adult Recipients Using UW Solution*

Indication	No. of Patients
Alcoholic cirrhosis	72
Chronic active hepatitis	23
Primary biliary cirrhosis	19
Malignancy	18
Sclerosing cholangitis	17
Cryptogenic cirrhosis	10
Hepatitis B	9
Inborn errors of metabolism	7
Fulminant hepatic failure	4
Other	5
Total	184

five livers were procured by our team. One hundred thirty were retrieved from our procurement area and 138 were from outside our procurement area. Sixty-seven livers were sent to other centers, whereas 20 livers were procured by other teams and sent to our center.

The method of organ retrieval has been described previously.[7] Briefly, after dissection of the liver or liver and pancreas, the aorta was cannulated and UW solution was used for intra-aortic perfusion as well as for *ex vivo* perfusion after the organs were removed. Likewise, the gallbladder and the common bile duct were flushed with UW solution, which is important for preservation of bile duct epithelium.[8] The recipient operation usually began at 8:00 A.M., unless the condition of the recipient was critical, in which case the operation was initiated immediately on return of the retrieval team. All adult patients were transplanted with the use of veno-veno bypass; however, this was not used in pediatric recipients. Indications for liver transplantation in adults are shown in Table 1 and for children in Table 2. The UNOS urgency classification for the adult and pediatric recipients is shown in Table 3. Thirty-five pediatric recipients received a reduced-sized liver: nine right lobes, nineteen left lobes, and seven left lateral segments. A quadruple immunosuppressive protocol was used that included antilymphocyte globulin, OKT3 (Orthoclone; Ortho, Rariton, NJ), azathioprine, prednisone, and cyclosporine, unless the patients were entered in the prospective randomized FK506-cyclosporine trial. The distribution of preservation times for the livers in this series is shown in Figure 1. The mean preservation time was 12.7 ± 4.4 hours.

TABLE 2. *Indications for Primary Liver Transplantation in Pediatric Recipients Using UW Solution*

Indication	No. of Patients
Biliary atresia	37
Cryptogenic cirrhosis	4
Fulminant hepatic failure	4
Chronic active hepatitis	2
Neonatal hepatitis	2
Cystic fibrosis	2
Other	5
Total	56

TABLE 3. *UNOS Status of University of Wisconsin Liver Transplant Recipients 1987–1991*

Status I	Status II	Status III	Status IV
10.2%	19.3%	26.7%	43%

Combined Pancreas/Kidney Transplantation

There have been 163 combined pancreas/kidney transplants performed during the past 4 years. The surgical techniques have been previously described,[9] and all but 10 pancreas transplants (enteric drained) were performed using the bladder drainage technique. Recipients were all juvenile diabetics with end-stage renal failure. The distribution of preservation times for the pancreas are shown in Figure 2. The mean pancreas preservation time was 17.2 ± 4.4 hours and that of the kidney was 19.2 ± 4.3 hours. Almost all recipients returned to the transplant unit after surgery, and only 3% required a short stay in the intensive care unit, primarily because of cardiac instability. Immunosuppression also consisted of quadruple protocol as described above.

Cluster Transplantation

Seven patients received a cluster transplant consisting of the liver, pancreas, and a portion of the duodeum as described by the Pittsburgh group.[10] The average preservation time for the cluster organs was 11.3 hours (range, 6.5–18).

Organization of the Operating Room Schedule

An example of the usual method of scheduling the operating room for multi-organ donor transplants is shown in Table 4. Once a multi-organ donor has been identified, the operating room staff is immediately notified and an operating room is made available at 8:00 A.M. for the liver

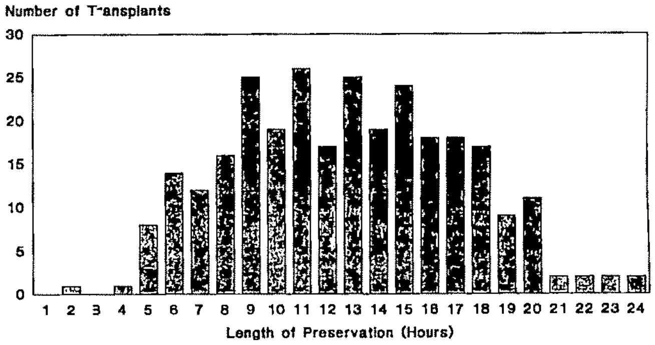

FIG. 1. Distribution of 288 liver transplants preserved with UW cold storage solution.

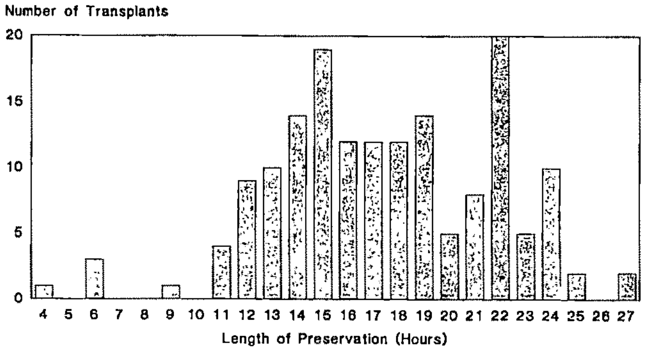

FIG. 2. Distribution of 163 pancreas transplants preserved with UW cold storage solution.

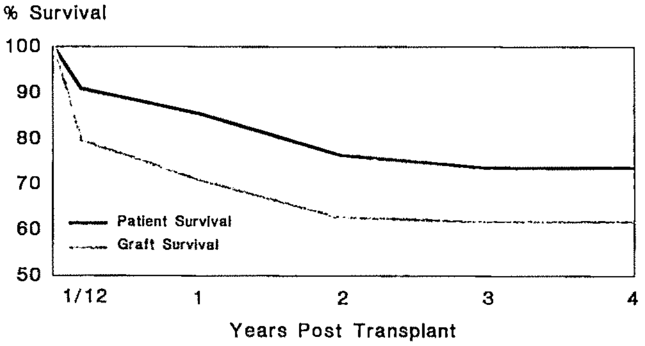

FIG. 3. Actuarial patient and graft survival in 288 liver transplants using UW cold storage solution.

transplant. The pancreas/kidney transplant follows in the next available operating room, and the second kidney from the multi-organ donor is usually transplanted the following morning at 8:00 A.M.

Results

Liver Transplantation

Figure 3 shows the 4-year actuarial patient and graft survival. One-month patient and graft survival was 91.4% and 80.2%, respectively. Patient survival at 1 and 4 years was 86% and 74%, respectively, whereas graft survival was 71% and 62%, respectively. The incidence of primary nonfunction (PNF) was 6.6%; hepatic artery thrombosis, 6.3%; bile duct stricture, 2.4%; and retransplantation was required in 16.0% of the recipients. There were no differences in the rates of PNF, hepatic artery thrombosis, or bile duct stenosis in livers preserved for less than or more than 12 hours. Grafts preserved for less than 6 hours, however, showed less hepatocellular injury, as indicated by lower serum enzymes, including aminotransferases and lactate dehydrogenase, than in livers preserved for 12 hours or more ($p < 0.05$). Before transplantation, livers procured between 1987 and 1990 were analyzed histologically by biopsy, but the transplant was performed, irrespective of the biopsy results. Beginning in January 1990, all liver biopsies that demonstrated severe macrovesicular or microvesicular steatosis were discarded because of the unacceptably high incidence of PNF in these livers.[11] Elimination of these unsuitable livers has reduced the rate of PNF from 9.2% to 4.0% (not significant). The length of stay in the intensive care unit after liver transplantation did not correlate with the length of preservation, but appeared to correlate with the condition of the patient before transplantation. Recipients that were in the poorest condition at the time of receiving a liver transplant had a longer stay in the intensive care unit.

Combined Pancreas/Kidney Transplantation

After combined pancreas/kidney transplantation, there was one initial nonfunction (0.6%) and two episodes of vascular thrombosis (1.2%). There were no episodes of PNF of the kidney, and only three patients required postoperative hemodialysis (1.8%) (Table 5). There was no difference in pancreas or renal allograft function or rate of graft-related complications in organs preserved for less than or longer than 12 hours. Figure 4 shows the 4 year actuarial patient and graft survival in simultaneous pancreas/kidney transplants. The actuarial patient survival at 4 years 1 month was 99.4% and 90.5%, respectively, whereas pancreatic and renal allograft survival at 1 month was 97.5% and 96.8%, and at 4 years was 83.0% and 83.4%, respectively. Because the UW solution is efficacious for all intra-abdominal organs, the results presented in this study include organs from muti-organ donors and included 132 combined pancreas, liver, and renal procurements. There were no differences in graft survival or development of graft-related complications when results with combined (multi-organ) procurements were compared with isolated (individual) organ procurements.

TABLE 4. *Usual Operating Room Schedule for Multiorgan Transplantation: University of Wisconsin Hospital*

Tuesday	Organ retrieval	Afternoon or evening Operating room notified by 7 PM
Wednesday	Liver transplant	8:00 A.M.
	Pancreas + kidney	First available room, usually 2:00–4:00 P.M.
Thursday	Kidney transplant	8:00 A.M. If liver or LRD transplant, first available room

TABLE 5. *Results of Early Pancreatic and Renal Function With UW Solution ($n = 163$)*

Outcome	No.
Immediate insulin independence	162 (99%)
Primary nonfunction	1 (0.6%)
Vascular thrombosis	2 (1.2%)
Graft pancreatitis	1 (0.6%)
Hemodialysis	3 (1.8%)

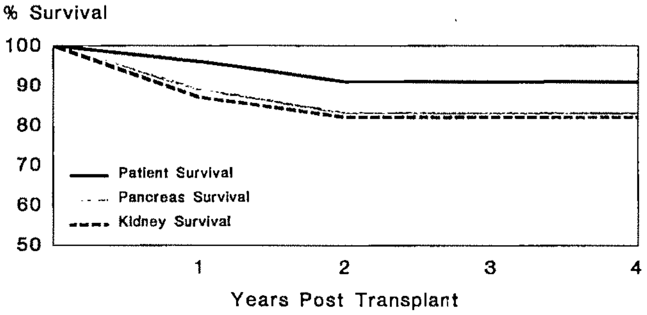

FIG. 4. Actuarial patient and graft survival in 163 simultaneous pancreas-kidney transplants using UW cold storage solution.

Cluster Transplantation

Our experience in cluster operations is summarized in Table 6, which shows the indications for surgery, patient survival, and cause of death. All recipients of a cluster transplant had immediate function of the grafts.

Discussion

During the past 4 years, we have used the UW solution for cold storage preservation of the liver, kidney, and pancreas. This method of preservation has allowed extended periods of preservation without compromising allograft function or increasing the rate of graft complications when compared with shorter periods of preservation. The availability of this solution for organ preservation has facilitated reduced-sized liver transplantation, organ cluster transplantation, and combined procurements of multi-organs with a greater margin of safety than previously achieved with other solutions.

Recently, it has been reported[12,13] that the incidence of PNF and the need for retransplantation in liver transplantation increases with increasing preservation time. Figure 5 depicts the incidence of PNF in our series according to the length of preservation. Although a slight trend of increasing PNF with increasing preservation time was seen, this difference was not statistically significant. We have noted, however, that the longer a liver is preserved, the greater the likelihood for higher levels of liver enzymes, although we have not seen a higher incidence of PNF. Elevated liver enzymes also appear to occur more frequently when the liver is procured from an older organ donor (older than 50 years) than in the younger organ donors. Primary nonfunction does correlate significantly with severe steatosis and for this reason, we currently perform biopsies on all donor livers before implantation and discard livers with severe steatosis or other significant pathology. Similarly, an evaluation of the donor pancreas before transplantation may disclose pancreatic abnormalities (fibrosis or chronic pancreatitis) that are contraindications for pancreas transplantation.

The availability of a method to extend the preservation of all intra-abdominal organs has not only contributed to increased usage of organs, improved logistics of organ sharing and an opportunity for reduced-sized liver and cluster transplantation, but also can make the transplant a semi-elective procedure. Semi-elective liver and pancreas transplantation has had a tremendous impact on anesthesia, operating room scheduling, and surgical personnel. We do not have anesthesiologists in our institution that are assigned to our transplant program; instead all anesthesia staff are assigned on a rotational basis. Performing the transplants during the daytime hours provides our transplant team with a complete complement of anesthesiologists that might not be available if the operations were performed late at night. Furthermore, the advantage of a daytime, regularly scheduled procedure, impacts significantly on the blood bank, which is fully staffed during the transplant. The surgical team also benefits from the capability of performing a transplant as a semi-elective procedure. The staff, fellows, and residents are, in general, well rested, which is more conducive to a long transplant operation. Additionally, the procurement team can rest between the time of the donor and recipient operations. Scheduling the transplant as a semi-elective procedure allows operating rooms to be used at night for trauma and other truly emergency procedures.

The most important contribution of the UW solution

TABLE 6. *Diagnosis and Outcome of Patients Undergoing a Cluster Transplant*

Patient	Age	Diagnosis	Outcome
1	43 yr	Cholangiocarcinoma with positive regional nodes	Died 21 mo Recurrent disease
2	36 yr	Cholangiocarcinoma with positive regional nodes	Died 11 mo Recurrent disease
3	62 yr	Metastatic carcinoid	Died 19 mo Recurrent disease
4	42 yr	Metastatic gastrinoma	Alive 19 mo
5	57 yr	Metastatic islet cell tumor	Alive 11 mo
6	43 yr	Alcoholic cirrhosis, diabetes, multiple previous surgeries	Died 2 mo Graft *vs.* host disease
7	6 mo	Biliary atresia, diabetes	Alive 2 mo

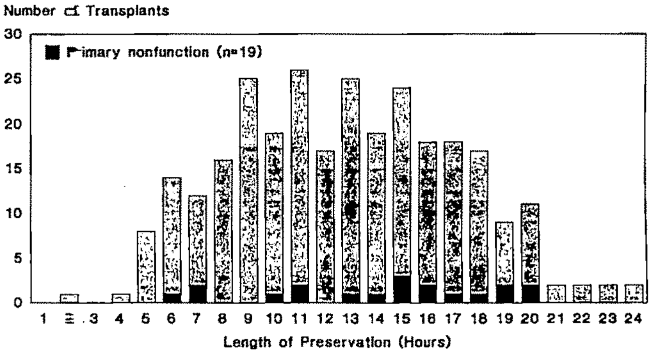

FIG. 5 Incidence of primary nonfunction in 288 liver transplants according to length of preservation.

TABLE 7. *University of Wisconsin OPO Donor Statistics 1986–1990*

Year	No. of Donors	Multiorgan	% Multiorgan	Kidney	Liver	Pancreas	Heart–Lung
1986	70	42	60%	138	10	25	7/0
1987	75	32	43%	142	17	11	16/0
1988	76	50	66%	141	45	23	16/1
1989	72	56	78%	138	51	45	32/2
1990	66	51	77%	120	54	38	22/0
1991*	68	47	69%	118	46	37	23/1

* As of November 12, 1991.

to clinical transplantation has been the capability to increase the use of scarce donor organs, thus increasing the number of patients that can receive a transplant. This is a consequence of the increased preservation time available when this solution is used. Also, recipients can remain at home while awaiting a transplant and have time to arrive at the hospital once an organ is obtained. Recently, several of our liver and pancreas recipients have traveled up to 2000 miles after they have been notified of a potential donor. Previously, patients were required to live in Wisconsin while awaiting a suitable donor organ. A further advantage is that all donors (except possibly older donors) can be considered for multi-organ donation because there is sufficient time before transplantation to examine the organs for suitability for transplantation.

The results in Table 7 show how the use of the UW solution has affected organ procurement in our Organ Procurement Organization. There has been an increase in the number of organs (especially the liver) procured since the introduction of the UW solution at our center. Although there are many problems left to be solved in organ transplantation, the shortage of donor organs continues to be one of the most pressing problems.

From a clinical standpoint, the UW solution has made a significant contribution to organ transplantation at our center as well as at other centers. Undoubtedly there will be improved methods of organ preservation in the future. Although the liver, kidney, and pancreas can be safely preserved for times that currently meet most clinical needs (24 to 40 hours), effective preservation of the heart and lung for similar times has not been consistently obtained. The UW solution may be safe for extended heart preservation (12 to 15 hours) as indicated in some preliminary studies[14,15]; however, a clear demonstration of what is needed to extend heart and lung preservation to 24 or more hours has not been presented.

Potential advantages exist if methods can be developed that extend clinical organ preservation beyond its current limitations. Truly long-term preservation could result in an increase in donor tissue matching, provide an opportunity to prepare a recipient for a particular organ, allow the establishment of organ banks, reduce the incidence of PNF or delayed graft function, and provide an opportunity for immunoalteration of the organ and reduce the incidence of rejection. The accomplishment of these goals will depend on fundamental research that defines the mechanisms of injury to cold-stored organs and provides a list of potentially beneficial therapeutic regimens necessary to suppress the injury.

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DISCUSSION

DR. RONALD W. BUSUTTIL (Los Angeles, California): Dr. Britt, Dr. Jones, Ladies and Gentlemen, Dr. Belzer and his colleagues are to be congratulated on this most important advance in organ preservation. University of Wisconsin (UW) solution has had a dramatic impact on all solid-organ transplantation, but none is more evident than on the liver. The modern era of liver replacement began in 1983, when the National Institutes of Health consensus conference showed that liver transplantation should be considered a therapeutic procedure for patients with end-stage liver disease. Since that time, there have been three seminal advances that have elevated liver transplantation to not only a safe and effective procedure but one that is available on a wide geographic scale. These include (1) refinements of the operative technique, particularly the use of venovenous bypass, which has allowed many of these operations to be performed within 5 or 6 hours with no blood product replacement; (2) the use of cyclosporine, and (3) the availability of UW solution for organ preservation. I remember very clearly in 1987 when Dr. Belzer presented his preliminary report on clinical liver preservation at the meeting in Pittsburgh. The concept of reliably extending hepatic preservation beyond 12 hours and thus converting liver transplantation to a semielective procedure really seemed too good to be true. Those of us who only knew liver transplantation as an emergency operation that required perfect timing between donor procurement and recipient hepatectomy so as not to extend the ischemia beyond 6 to 8 hours were really overwhelmed by the prospects of this new solution. These prospects have now been realized, and UW solution has virtually replaced all other preservation modalities in the United States and much of Europe for extrarenal preservation. The results reported today by the Wisconsin group are truly outstanding. Despite a mean preservation time of 12.7 hours, the primary nonfunction rate is 6.6%. The 1-year patient and graft survival rates are 86% and 71%, respectively. Hepatic artery thrombosis is 6.3%, and bile duct stricture rate is 2.4%.

But are these results specific to the center that introduced this method of preservation? In May of 1988 we performed at UCLA a prospective trial of UW solution *versus* the standard method of preservation, Eurocollins solution. There were 114 patients that we studied that were matched for donor and recipient characteristics. The UW group had a mean preservation time of 11.5 hours. The group that received Eurocollins solution had a mean preservation time of 4.9 hours. Complications were virtually identical despite the more than doubling the preservation time with the UW solution. There was one incidence of primary nonfunction. There was a similar incidence of hepatic artery thrombosis, but interestingly enough, none of the patients with UW solution that had this complication required retransplantation. And the survival rates, again, despite the prolonged preservation in UW solution, were the same as with Eurocollins solution, 87% and 84%, respectively.

Despite the advantages that UW has provided in both graft preservation and in the logistics of liver transplantation, I have some concerns about extending the ischemia time much beyond 12 hours. Although the authors did not show a statistical significance in the incidence of primary nonfunction with ischemia above or below 12 hours, the trend is clearly there. Of 19 primary nonfunctions, 13 or 68% percent occurred with the preservation time of more than 12 hours. Furthermore, the donor older than 55 years of age, in our experience, will not tolerate long ischemia times, and we prefer to transplant them within 6 hours. Finally, the issue of biliary strictures is important. We have observed seven intrahepatic duct strictures, none associated with hepatic artery thrombosis, in 792 liver transplants. Although this is a low incidence, cold ischemia time in all of these seven cases exceeded 12 hours.

I would like to conclude by asking Dr. Belzer three questions: (1) What donor or recipient characteristics, if any, would influence you to avoid ischemia beyond 12 hours? (2) Do you believe that a back-table flush is necessary over and above an *in situ* flush, and is it necessary to irrigate the biliary tree with UW solution? (3) Do you believe that the current UW is well suited for small intestinal preservation or should it be modified? And what would be your limits of ischemia for the bowel? Again, I would like to congratulate you on a landmark contribution to transplantation. Thank you.

DR. GIL DIETHELM (Birmingham, Alabama): Dr. Britt, Dr. Jones, Members and Guests, I am pleased to have the opportunity to discuss Dr. Belzer's paper regarding the use of University of Wisconsin (UW) solution for the liver, kidney, and pancreas transplantation. This is a particularly important paper, and the results come from the transplant center, as you know, that has developed this solution. To me, it is the first major advance in transplant preservation since 1969. And as you have heard from Dr. Busuttil, it immediately had a major impact on the entire field. It allowed us at the University of Alabama, using Dr. Belzer's solution and his technique of pulsatile perfusion, to preserve kidneys safely up to 50 and 55 hours. We use pulsatile perfusion and I believe this has had a major impact on improvement of our graft survival and decreasing the risk of acute tubular necrosis (ATN). When we used cold storage with the solution, our average time was 24 hours of ischemia, and we had a 24% incidence of ATN. When we went to pulsatile perfusion with the UW solution, we extended the preservation time to 32 hours, and we decreased the ATN rate to 8%. Thus we did two things. We decreased the ATN rate and we advanced the preservation time. I have long been impressed with the observation that preservation from kidneys in young people can be carried out for quite a time. Perhaps it is the young organ or young cell. As the donor age increases, the ability to carry out prolonged preservation seems to diminish. For example, in our institution, if the patient is older than 50 or 55 years of age, we would not attempt to carry out preservation for 45 hours if we could avoid it, and we certainly could. We have used patients aged 65 and 70 years, but again, we try to decrease the preservation interval to 12 or 15 hours. So I wonder if the age of the donor does play a role in the prolongation or the limitations of prolonging transplant ischemic interval, and I would appreciate Dr. Belzer's comment. Dr. Belzer made a small comment that might have gone unnoted. But for those of us that are involved in multiorgan transplantation, the ability to start a case at 8:00 in the morning, a liver case, and combine it with a kidney–pancreas a few hours later using daytime personnel, and daytime operating rooms, is an enormous step forward.

I think also Dr. Belzer mentioned—and, I believe, very importantly—the value of a liver biopsy. The same is true with a kidney biopsy. And if there is a question of a marginal kidney or liver donor, that can be resolved with a biopsy in many instances and allows one to abort the transplant if you wish or to go ahead. Dr. Belzer also mentioned the hostile environment of the recipient patient and the role it might play in nonfunction. I believe that is a very important comment, and I think that in many instances so-called nonfunction of the recipient organ has nothing to do with the preservation interval but, rather, the immunologic environment into which that organ is placed.

For example, two kidneys from the same donor placed in the two recipients with approximately the same preservation time does not guarantee the same immediate function. Therefore, the recipient patient himself or herself does play a role with, as he described, the hostile environment.

I would like to ask Dr. Belzer a second question pertaining to the composition of the UW solution. Fred, what components do you consider to be the most important in your solution? I recognize that is a difficult question. And then what alterations might be possible to extend the current preservation time? In light of that, do you have an impression as to the ultimate interval of organ preservation using the hypothermic conditions? In other words, is there an obstacle that 4 to 10 degrees of hypothermia might present that would be the obstacle in preservation? Can you go 4 days, 5 days, 10 days, longer?

I would like to thank Dr. Belzer for allowing me to review the manuscript in advance. But also would like to thank him especially, as a transplant surgeon, for the important contributions he has made to the field of organ preservation and transplantation. Thank you.

DR. F. O. BELZER (Closing discussion): First, I would like to thank the discussants for their kind comments. Dr. Busuttil had several questions. Number one, about a back-table flush, especially of the bile duct. We have just submitted an editorial to *Transplantation* as we have never published the management of the common duct in great detail. Most people flush the gallbladder at the time of donor procurement. I have been amazed as a general surgeon now that we do donor hepatectomies to realize how low the cystic duct in many cases enters the common duct, although we divide it right at the edge of the pancreas. Fifty percent of the time you are looking at two lumens. We have always flushed out the bile duct with University of Wisconsin solution on the back table.

If you just wash out the gallbladder, you leave the bile in the entire hepatic ductal system, and bile is a very caustic material. I think this has been one of the problems of bile duct strictures that the bile duct itself was never adequately preserved. We have had imported livers to be quite honest, and I have a picture of this where the liver when removed from the bag was covered with bile. Thus, it is understandable why bile duct strictures can occur.

As far as donors older than the age of 50, to me as I am getting older, over 50 is still pediatric, and I think some of the people in this audience may feel the same. But as far as liver transplantation, there is no question that the older donor will give you higher enzymes, and I personally think would also give us higher primary nonfunction. Thus, I agree with Dr. Busuttil that in an older liver, 50 to 56, we should try to keep the preservation down to a minimum.

Regarding the small bowel, we are just doing a study in the laboratory to look at the limits of preservation. I think that the bowel is pretty resistant to cold ischemia, but only further studies will show the limits of preservation. Dr. Diethelm asked the same question of the donor age. We see the same thing in kidneys. Kidneys from older donors don't work as well as from young donors, and I think this is true for the liver and also for the pancreas. In the older pancreas, although it works and the patient is normoglycemic, the serum amylase and the urine amylase will be quite different than in the younger donor. Dr. Diethelm also emphasized the importance of recipient factors, the so-called hostile environment. In kidney transplantation we have accepted 6% primary nonfunction for 20 years. We called it rejection or we said there were technical problems. In livers, we suddenly want to get 100% immediate function. Dr. Diethelm actually published a paper in the *Annals of Surgery* showing that if the same donor provided two kidneys and if one kidney did well and the other kidney did poorly, that the final outcome of the second kidney was usually poor because there was another reason why the kidney did not work, rejection or something in the recipient. The problem in the laboratory is that we are studying normal dogs. We are trying to develop a chronic liver failure model so that we can do the transplant in the dogs the same way that we do transplants in patients with end-stage liver disease.

What alterations would we make in the University of Wisconsin solution? There are obviously ways to improve it. The problem is that it would be very difficult to introduce minor changes because you would have to go through an FDA-approved trial again. So I think that any changes must show major improvement rather than minor changes. Again, I appreciate the time to answer these questions.

Pancreas Transplantation

An Initial Experience With Systemic and Portal Drainage of Pancreatic Allografts

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Pancreas transplantation has evolved dramatically since its introduction in 1966. As new centers for transplantation have developed, the evaluation of complications associated with pancreas transplantation has led to advances in surgical technique. Furthermore, surgical alterations of the pancreas resulting from transplantation (systemic release of insulin and denervation) are of unproven consequence on glucose metabolism. Since 1988, the authors have performed 21 transplants (16 combined pancreas/kidney, 3 pancreas alone, which includes 1 retransplantation, 1 pancreas after previous kidney transplant, and 1 "cluster") in 20 patients aged 18 to 49 years; mean, 35 ± 1 years. Overall patient survival is 95%. Three pancreatic grafts failed within the first year because of technical failure; one additional pancreas was lost to an immunologic event on postoperative day 449, for an overall pancreatic graft survival of 81%. No renal grafts were lost. To evaluate causes of graft failure, demographic data were compared, which included age and sex of the donor and the recipient, operative time, intraoperative blood transfusion, and ischemic time of the graft. No statistically significant differences were found between groups except for ischemic time (11.7 ± 6.4 hours for the technical success group *versus* 19.8 ± 3.7 hours for the technical failure group; $p < 0.05$ by unpaired Student's t test). Quadruple immunosuppression was used, which included prednisone, cyclosporine, azathioprine, and antilymphoblast globulin. A mean of 1.2 (range, 0 to 3) rejection episodes per patient occurred. Mean hospital stay was 24 ± 11 days. Surgical and infectious complications were evaluated by comparing the technical success (TS) group (n = 17) with the technical failure (TF) group. Surgical complications in the TS group revealed a mean of 1.3 episodes per patient, whereas the TF group had 3.7 episodes per patient. The TS also had a reduced incidence of infectious complications compared with the TF (1.7 *versus* 4.3 episodes per patient). Cytomegalovirus was common in both groups, accounting for 11 infectious episodes, and occurred on a mean postoperative day of 38. Mean postoperative HbA1C levels dropped to 5 ± 1% from 11 ± 3%. The authors developed a new technique that incorporates portal drainage of the pancreatic venous effluent in three recipients. Preoperative metabolic studies disclosed a mean fasting glucose of 211 ± 27 mg/dL and a mean stimulated glucose value of 434 ± 41 mg/dL for all patients; the mean fasting insulin was 23 ± 4 μU/mL. After operation, the systemic drainage groups had mean fasting and stimulated glucose values of 87 ± 7 mg/dL and 151 ± 11 mg/dL; mean fasting and stimulated insulin values were 56 ± 10 μU/mL and 190 ± 26 μU/mL, respectively. The portal drainage group had mean fasting and stimulated glucose values of 91 ± 5 mg/dL and 135 ± 28 mg/dL; mean fasting and stimulated insulin values were 34 ± 1 μU/mL and 88 ± 27 μU/mL, respectively. In summary, pancreas-renal transplantation can be safely employed with an acceptable complication rate for the treatment of type I diabetes and may provide a euglycemic state. Systemic drainage of the pancreatic graft, however, is associated with hyperinsulinemia, which has unknown consequences. An alternative technique with portal drainage appears to reduce peripheral levels of insulin and has unproven long-term consequences on the potential detrimental effects of hyperinsulinemina.

PANCREAS TRANSPLANTATION HAS become an increasingly common therapeutic option for the treatment of type I diabetes mellitus. According to the International Pancreas Transplant Registry, 1415 pancreas transplants have been performed worldwide from 1988 to 1990 and over 3000 since 1966.[1] Advances in medical technology have resulted in new treatment advances for diabetes, including more efficient means of monitoring blood glucose, as well as continuous insulin infusion pumps. Consistent normoglycemia has been ac-

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complished in the minority of patients, however, who also run the risk of intermittent episodes of hypoglycemia. Thus, continuous normalization of blood glucose values with successful transplantation of the whole pancreas has become a more accepted therapeutic option. This has led to the development of new transplant centers worldwide and a markedly increased number of transplants performed annually. With advances in surgical techniques, increasing experience with simultaneous pancreas–kidney transplants, and more sophisticated methods of immunosuppression, 1-year graft survival now approaches 80%.[1]

The traditional method of heterotopic placement of the pancreas allograft necessitates surgical alterations in the revascularized graft, which include (1) systemic drainage of the venous effluent, (2) denervation of the graft, and (3) potential reduction in beta-cell mass with organ preservation. The benefits and the consequences of this surgical manipulation have not been fully evaluated. Furthermore, with increased success of pancreas transplantation, attention also has become focused on the effects of the transplant on carbohydrate metabolism and glucoregulation.

The first pancreas transplant was performed at the University of Virginia in 1988. As of September 1991, 21 pancreas transplants have been performed at our institution. We evaluated our clinical experience and specifically examined the associated surgical and infectious complications that accompany transplantation and consequent immunosuppression. Additionally, we analyzed the effect of pancreatic transplantation on carbohydrate metabolism and compared early findings of differences between systemic and portal drained pancreatic allografts. An alternative technique is introduced, which drains pancreatic venous effluent into the portal system and appears to decrease the peripheral hyperinsulinemia associated with systemic drainage. The latter technique also appears to eliminate complications associated with draining pancreatic exocrine secretions into the bladder.

Materials and Methods

The case histories of 20 patients who received pancreas–kidney transplants were retrospectively reviewed for data on patient and graft survival, demographic information, and postoperative surgical and infectious complications. Graft survival is defined by freedom from exogenous insulin. Surgical complications were included that required readmission or additional operative or invasive procedures. Infectious complications included those infections that required administration of antibiotic therapy, readmission, or positive cultures. Selected patients underwent provocative tests for glucoregulatory parameters as described below.

Patient Population

Twenty patients received 21 pancreas transplants, with one patient requiring retransplantation. There were 10 men and 10 women. Nineteen of the patients had type I diabetes mellitus. One patient was an 18-year-old woman with hepatocellular carcinoma with local extension that included the pancreas. She received a combined liver and pancreas "cluster" transplant. Because she was not transplanted for diabetes and most of her complications were related to her liver transplant, she is only included in the data for patient and graft survival. She presently has a functioning pancreatic graft and is euglycemic; however, she has evidence of recurrence of her original disease process with metastases.

The mean age of all recipients was 34.1 ± 7.3 (range, 18–40) years. All patients were required to undergo cardiac evaluation before transplant. In addition to the aforementioned cluster transplant, 16 patients received simultaneous pancreas–kidney grafts (SPK), two patients received a pancreas transplant alone, and one patient received a pancreas transplant 4 years after a successful living-related donor kidney transplant. One patient in the pancreas–kidney group required retransplantation with a second pancreatic graft.

Organ Donors

The age of the organ donors ranged from 14 to 39 years (mean, 23.9 ± 6.7 years; 19 men and 2 women). All donors were multiorgan donors, with concomitant hepatectomy also performed in most cases. The technique used for combined liver–pancreas procurement was a modification of the procedure that has been described previously by Marsh et al.[2]

Organ Preservation

One hour before the time the donor arrived in the operating room, 1 g erythromycin base, 1 g neomycin base, and 2 million units of nystatin were given through the nasogastric tube. Before vessel cannulation, 30,000 units of heparin were given systemically. Approximately 2 L University of Wisconsin solution was flushed through the aortic cannula and 1 L lactated Ringer's followed by 1 L University of Wisconsin solution was flushed through the venous cannula with low pressure. Cold topical solution also was applied into the abdomen. After pancreatectomy, the pancreas was flushed with an additional 100 mL University of Wisconsin solution. The graft then was secured in a sterile plastic bag and kept on ice until ready for reimplantation. The donor kidney was preserved in the same manner and also stored in a sterile fashion until ready for reimplantation.

Surgical Procedures

For the simultaneous pancreas kidney transplants, two different surgical procedures were used. The first technique, currently the most common technique used nationwide, has been described previously.[2] A lower midline incision was the preferred approach. Briefly, the right iliac fossa was prepared for the pancreatic graft. Complete mobilization of the right common iliac artery was performed, which usually required ligation of the hypogastric artery. The iliac vein was similarly prepared with ligation of small branches. Because most grafts were harvested during multiorgan harvests with hepatectomy, the pancreatic arterial supply was reconstructed before reimplantation using a Y-graft from the iliac artery with the internal and external branches from the donor anastomosed to the superior mesenteric and splenic arteries of the graft. Revascularization then was performed with an end-to-side anastomosis of the portal vein to the external iliac vein. An end-to-side anastomosis was performed with the attached donor iliac Y-graft to the external iliac artery. Bladder drainage was accomplished by duodenoneocystostomy with a duodenal segment and a two-layer handsewn anastomosis, as described by Nghiem and Corry[3] (Fig. 1). The duodenal contents of the graft were aspirated before implantation, and the contents were sent for culture. All patients received perioperative antibiotics for 72 hours. If the duodenal content cultures were negative, then the antibiotics were discontinued. If the cultures were positive, then the antibiotics were continued for 7 days. Lastly, the kidney was placed in the left iliac fossa with minimal mobilization of the common iliac vessels. The artery and the vein were anastomosed in an end-to-side fashion. A ureteroneocystostomy then was developed anteriorly.

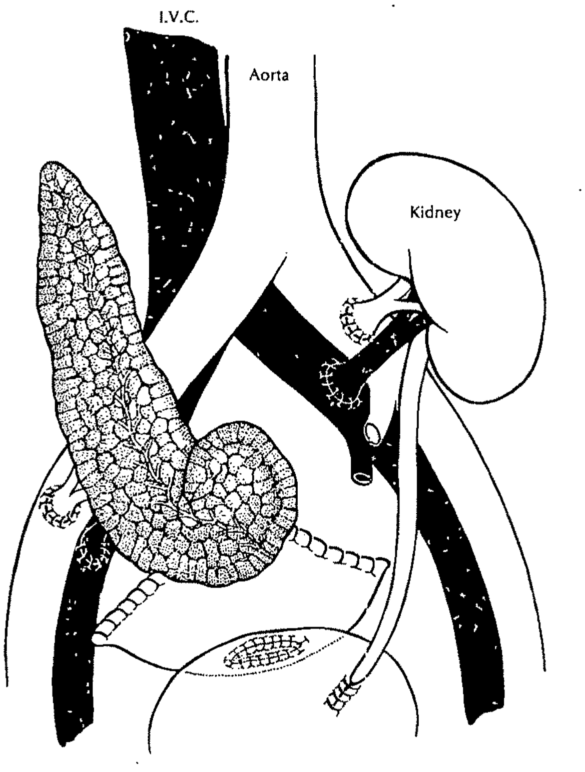

FIG. 1. Technique of pancreas-kidney transplant with systemic drainage. This technique has been described by Sollinger et al.[18] and includes placement of the pancreatic graft in the right iliac fossa. The donor portal vein is anastomosed to the recipient iliac vein, resulting in systemic drainage of pancreatic venous effluent. Further details are given in the text.

An alternative technique was performed in three of the 16 patients who received SPK. This method was a modification of several techniques reported by others.[4-12] This technique was adopted for a multitude of reasons, including profound metabolic acidosis secondary to bicarbonate loss with bladder drainage of pancreatic secretions as well as a significant hyperinsulinemia associated with systemic venous drainage. Briefly, a midline incision was used and the recipient proximal splenic vein was isolated at the base of the transverse mesocolon. The aorta also was cleared for vascular anastomosis. The donor pancreas then was placed in a paratopic position, placed parallel to the aorta. The donor portal vein was anastomosed in an end-to-side fashion to the recipient proximal splenic vein. The artery was revascularized through an end-to-side anastomosis to the aorta, using a donor iliac arterial Y-graft described above. A duodenojejunostomy was performed to the proximal jejunum (Fig. 2). Lastly, the kidney transplant is performed in the usual fashion in the left iliac fossa.

Recipient Immunosuppression

Induction immunosuppression consisted of quadruple therapy for those patients receiving simultaneous pancreas-kidney transplants. Antilymphoblast globulin was used for 7 to 14 days, starting on postoperative day 1 at a dose of 20 mg/kg/day. Prednisone was administered in a bolus of 2 mg/kg/day and rapidly tapered to a dose of 0.5 mg/kg/day, which results in a dose of approximately 30 mg/day, maintained for long-term immunosuppression. Azathioprine was administered with an initial dose of 5 mg/kg/day and then lowered to 2.5 mg/kg/day and adjusted accordingly to maintain a white blood cell count greater than 4×10^9 cells/L. Cyclosporine was not administered until day 6 in those patients receiving SPK. When started, it was given at a dose of 8 mg/kg/day and rapidly tapered to 1 to 3 mg/kg/day to maintain a therapeutic cyclosporine drug level of 200 ng/mL by high-pressure liquid chromatography methodology. If the patient received only a pancreas transplant or had received a living related donor kidney in the past, cyclosporine was

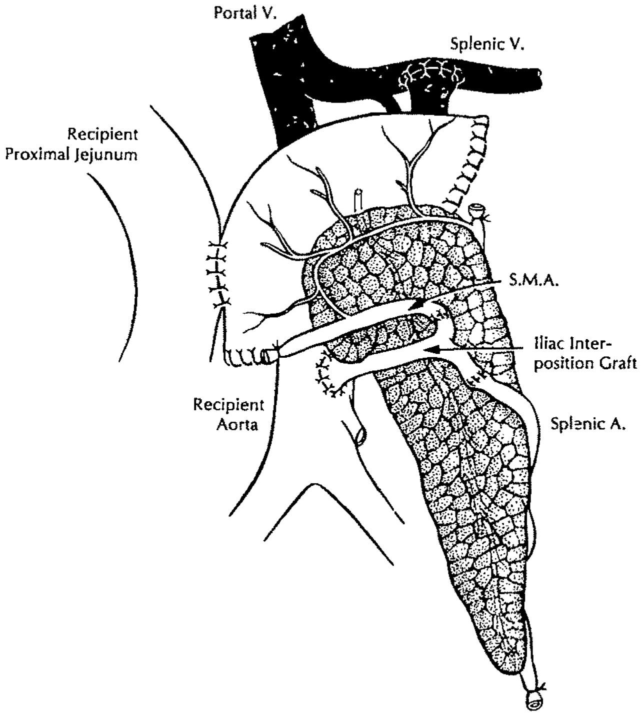

FIG. 2. Technique of pancreas–kidney transplant with portal drainage. The pancreatic graft is placed in a paratopic position at the base of the transverse mesocolon. The donor portal vein is anastomosed to the recipient proximal splenic vein, and the artery is anastomosed to the aorta via a donor iliac artery Y-graft. Pancreatic exocrine drainage is via a duodenojejunostomy. Further details are given in the text.

initiated immediately. Long-term immunosuppression as an outpatient consists of 1 to 3 mg/kg/day of cyclosporine administered orally to maintain adequate drug levels. Also, prednisone at approximately 30 mg/day and azathioprine, usually at a dose of 1 to 2.5 mg/kg/day, was given on a regular basis. The azathioprine must be withheld if the patient becomes neutropenic.

Diagnosis and Treatment of Rejection

Rejection was monitored with urinary amylase, serum glucose levels, and serum creatinine levels in patients who received SPK with urinary drainage of pancreatic exocrine secretions. If the serum creatinine rises, a biopsy can be performed to confirm rejection, because this usually occurs before the urinary amylase decreases. We did not perform pancreatic biopsies in our patients to histologically confirm the diagnosis of rejection because of the risk of pancreatic fistula. Pancreas biopsy has been used routinely by other groups using the bladder drainage technique.[13,14] The patients who received a paratopic pancreas transplant also received a simultaneous kidney transplant. Serum glucose and serum amylase levels were monitored; however, the diagnosis of rejection was primarily established through monitoring of the serum creatinine level and subsequent renal biopsy if indicated.

Rejection episodes were treated by a temporary increase in the prednisone dose with a rapid taper or with a 10- to 14-day course of anti-OKT3 monoclonal antibody at a dose of 5 mg/kg/day. Prednisone can be used as a single agent if the rejection episode is mild. However, most rejection episodes were believed to be moderate or severe, and the patients received both a steroid recycle and intravenous OKT3.

Metabolic Studies

Recipients of pancreas transplantation underwent metabolic and oral glucose challenge tests before operation and 6 to 12 months after operation. Every effort was made to perform these studies when the patients were clinically healthy, without evidence of rejection. All studies were performed in the University of Virginia General Clinical Research Center with the approval of the Human Investigation Review and under federal guidelines.

The 24-hour metabolic studies were initiated at 12:00 midnight, and thereafter, blood samples were drawn every hour for the next 24 hours. Samples for glucose, insulin, and C-peptide were evaluated at each time point. Glucose values were determined with a Beckman Glucose Analyzer II (Fullerton, CA). Insulin and C-peptide assays were performed by the University of Virginia Diabetes Center Core Laboratory facilities. During the course of the day, the preoperative patients were allowed to take their individual insulin doses. Meals (40 to 60% carbohydrate) were given at 7:30 A.M., 12:00, and 5:00 P.M. Additional standardized snacks were administered at 10:30 A.M. and 8:00 P.M.

The oral glucose tolerance test was performed after an overnight fast. Each patient then ingested 100 g glucose orally at 8:00 A.M. Two basal samples of blood were drawn before ingestion, followed by sample collection at 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes through indwelling catheters. Samples for glucose and insulin also were analyzed, as described above.

Statistical Calculations

Integrated responses for the oral glucose tolerance tests were calculated using the trapezoidal rule applied to each sampling time interval. The integrated responses then were divided by the number of minutes in the study from the time of the glucose challenge, yielding a mean integrated response per unit time.

Other data were analyzed using version 6.04 of the SAS statistical package for personal computers. Pairwise comparisons of means were made using Students unpaired *t* test. Comparisons of means of three or more groups were made using general linear modeling for analysis of variance with Duncan's multiple tests and least squares means for the determinations of significance between groups.[15] Results were presented as mean ± standard error of the mean except for demographic data, which were presented as mean ± standard deviation.

Results

Patient and Graft Survival

For all patients, the mean follow-up time was 526.6 ± 334.4 days (range, 58 to 1298 days). Three grafts were lost within the first year, for a 1-year graft survival rate of 86%. We have six patients who are 2 years out from their transplant, five of these are SPK and one patient is a pancreas transplant alone; all six of these grafts are functioning well. Kidney survival rate during that time is also 100%. One immunologic graft loss occurred on postoperative day 449. The pancreatic rejection occurred without simultaneous renal rejection in this patient. The other three graft losses were all nonimmunologic and were lost within the first 2 months of transplantation and could be attributed to technical reasons for graft failure. One graft was most likely damaged from a preservation injury, which resulted in a profound and persistent pancreatitis. A second graft was lost from an exocrine duct stricture, which ultimately resulted in an unrelenting pancreatitis and subsequent graft loss. Venous thrombosis was the cause of the third technical failure. The thrombosis rate in our series was 4.8%. Overall graft survival is now 81%. Of the three patients who underwent paratopic placement of their pancreatic graft, all have functioning pancreas and renal grafts. The patient who received a liver and a pancreas also has both grafts functioning well. Of the 15 renal grafts available for follow-up, all are functioning well, resulting in a 100% renal allograft survival. Mean postoperative serum creatinine was 1.4 ± 0.4 mg/dL.

Only one patient died after transplantation, resulting in a patient survival rate of 95%. The patient received a simultaneous pancreas–kidney transplant with bladder drainage. Both his kidney and pancreas initially were functioning well. However, on postoperative day 4, the patient had a decreased urinary amylase and was taken to the operating room for exploration to rule out venous thrombosis because noninvasive vascular studies could not adequately determine vascular flow to the pancreatic graft. The pancreatic graft was found to be mildly edematous, but vascular flow and duodenoneocystostomy were patent. In the recovery room, he suffered a cardiopulmonary arrest from which he was not able to be resuscitated. Autopsy showed no obvious cause of death and no evidence of myocardial infarction. His pancreatic and renal grafts were found to have no gross abnormalities.

TABLE 1. *Demographics*

Characteristic	All	Success	Failure
Age (yr)	34.8 ± 1.4	34.5 ± 5.6	36.3 ± 11.2
Sex (M/F)	10/10	8/9	2/1
Hospital days	24.4 ± 11.4	22.4 ± 10.7	36 ± 9.2
Donor age (yr)	23.4 ± 6.4	22.9 ± 5.5	25.7 ± 11.7
Operation time (hr)	7.1 ± 2.4	6.8 ± 2.1	9.1 ± 3.4
Units blood	1.8 ± 2.7	1.5 ± 1.6	3.7 ± 6.4
Ischemic time (hr)	13.0 ± 6.7	11.7 ± 6.4	19.8 ± 3.7*
Readmissions	2.1 ± 1.6	2.3 ± 1.6	0.5 ± 0.7

* $p < 0.05$ *vs.* success.
Mean ± SD.

Effect of Human Leukocyte Antigen on Graft Survival

All 21 organ donors were reviewed for human leukocyte antigen tissue typing. There was no correlation found between the patients with graft success and those with failure when evaluating the tissue typing. There was no evidence that human leukocyte antigen mismatch at any loci adversely affected graft survival.

Factors Contributing to Graft Loss

Data were analyzed that compared recipient age, donor age, donor sex, operative time, the number of intraoperative blood transfusions, the number of hospital days, and ischemic time (Table 1). No statistical differences were found between any of the factors except for ischemic time in relation to graft loss. The mean ischemic time for the grafts that survived was 11.7 ± 6.4 hours *versus* 19.8 ± 3.7 hours for the grafts that were technically unsuccessful ($p < 0.05$ by unpaired Student's t test). There were no statistically significant differences in demographic data between the portal and the systemic drainage groups.

Rejection

Eighteen patients were available for evaluation of rejection episodes (excluding the one death and the pancreas–liver "cluster" transplant). A total of 23 rejection episodes were diagnosed and treated. This resulted in a mean of 1.2 rejections per patient, with a range of 0 to 3. Two patients were not diagnosed with any episodes of rejection, and only one patient had three episodes. Rejection episodes were treated with steroids in nine episodes, OKT3 as a single agent in eight instances, and a combination of OKT3 and steroids in six cases of rejection. Treatment was successfully accomplished in all cases except in the instance of immunologic graft loss due to discontiguous renal and pancreatic rejection in one patient.

Surgical and Infectious Complications

The surgical and infectious complications are outlined in Table 2. We have subdivided the results into the technical successful grafts (n = 17) and the technical failures (n = 3). One patient is included in both groups because he received a second successful transplant after his initial pancreatic graft was lost to venous thrombosis. In the technical success group, surgical complications included two negative laparotomies, one for bleeding and one to rule out venous thrombosis. There were also two late small bowel obstructions, which resulted in laparotomy and lysis of adhesions. One patient suffered complication of radial artery catheterization. On postoperative day 1, he had pain and paresthesias in his right thumb, and arteriogram showed radial artery thrombosis with proximal propagation and an incomplete dorsal arch. He underwent emergent thrombectomy; however, later he required intra-arterial streptokinase. His thumb was subsequently revascularized except for the distal phalanx, which required amputation and placement of a split-thickness skin graft. He also developed a wound infection from a hematoma related to the use of streptokinase, but his vascular anastomoses and pancreatic graft tolerated the streptokinase well in the immediate postoperative period. Other surgical complications included one non–Q-wave myocardial infarction and one deep venous thrombosis and subsequent pulmonary embolus, which responded well to treatment. Other complications are listed in Table 2. There were nine total complications in seven patients in this group, which resulted in a mean of 1.3 surgical complications per patient.

TABLE 2. *Complications*

Technical successes (n = 17)	
Surgical complications (n = 7)	
Negative laparotomy	2
Small bowel obstruction	2
Urinoma	1
Perioperative MI	1
DVT resulting in PE	1
Wound dehiscence	1
Radial artery thrombosis	1
Total	9 (1.3/patient)
Infectious complications (n = 12)	
CMV virema	8
UTI	5
HSV (cutaneous)	4
Central line	2
Wound	1
Total	20 (1.7/patient)
Technical failures (n = 3)	
Surgical complications (n = 3)	
Abdominal abscess	2
Pancreatitis	2
Bleeding	2
Wound dehiscence	2
Cholestasis	1
Bladder stitch abscess	1
Penile prosthesis erosion	1
Total	11 (3.7/patient)
Infectious complications (n = 3)	
UTI	3
CMV viremia	3
Abdominal absecess	2
C. difficile colitis	2
CMV hepatitis	1
Pneumonia	1
HSV (cutaneous)	1
Total	13 (4.3/patient)

MI, myocardial infarction; DVT, deep vein thrombosis; PE, pulmonary embolus; CMV, cytomegalovirus; UTI, urinary tract infection; HSV, herpes simplex virus.

In the technical failure group, there were 11 surgical complications in three patients, for a mean of 3.7 surgical complications per patient. This differs greatly from the 1.3 surgical complications per patient in the technical success group. Two patients had persistent pancreatitis, which resulted in a variety of procedures, and the same two patients also developed intra-abdominal abscesses. One patient developed elevated liver function tests late in the complicated postoperative course and had severe cholestasis that required a percutaneous cholecystostomy. A patient with a urinary bladder stitch abscess experienced three episodes of *Pseudomonas aeruginosa* urinary tract infection until the retained suture became visible and was removed by cystoscopy. These are not included under the urinary tract infection category because they resulted from the stitch abscess and were not separate episodes. Additional complications are outlined in Table 2.

For infectious complications, in the technical success group, 20 infections were isolated in 12 patients, which showed a mean of 1.7 infection episodes per patient. In comparison, 13 infectious episodes occurred in the three patients in the technical failure group, for a mean of 4.3 infectious episodes per patient. Most infections in the technical success group were either cytomegalovirus (CMV) or herpes simplex virus. The herpes simplex viruses were all cutaneous lesions and were treated on an outpatient basis. The CMV usually required readmission to the hospital and treatment with gancyclovir. All CMV infections in both groups, 11 total episodes, were found on a mean postoperative day of 38. All CMV episodes were isolated in the blood, and one of those also resulted in CMV hepatitis in a patient in the technical failure group. The remainder of infections in the technical success group were minor and responded to antibiotic therapy.

The infections in the technical failure group are outlined in Table 2. Two patients developed intra-abdominal abscesses. The organisms isolated from these abscesses included *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Citrobacter freundii.* This group included three urinary tract infections in three patients, and three episodes of CMV, including one CMV hepatitis and one *Pseudomonas aeruginosa* pneumonia.

Most infectious complications in the technical failure group occurred during the initial post-transplant hospitalization. Overall, the readmission rate was 2.3 ± 1.7 readmissions per patient. The readmissions were usually associated with late infectious complications, including CMV and rejection episodes.

Recipient Metabolic Studies

Twenty-four-hour Metabolic Studies. Twenty-four-hour metabolic studies demonstrating glucose, insulin, and C-peptide levels for the preoperative patients (n = 18), and for seven patients with systemic drainage graft procedures, are depicted in Figure 3. For the preoperative patients, fasting glucose was 209 ± 19 mg/dL. Insulin values for this group did not peak with meals and most likely reflected individual exogenous insulin administration because the C-peptide levels were 0.009 ± 0.4 pmol/mL. Post-transplant mean fasting glucose was 103 ± 8 mg/dL, which was approximately one-half the value of the preoperative values. Insulin values demonstrated a fasting hyperinsulinemia of 42 ± 10 μU/mL and meal-stimulated hyperinsulinemia to 131 ± 34 μU/mL. C-peptide values were markedly increased with transplantation to a fasting level of 0.769 ± 0.7 pmol/mL and a meal-stimulated level of 1.1 ± 0.1 pmol/mL.

Oral Glucose Challenge: Systemic Versus *Portal Drainage.* The results of a standard oral glucose challenge comparing all preoperative patients (n = 18) with postoperative patients who were either systemically drained pancreatic allografts (n = 6) or portal drained pancreatic allografts (n = 3) are depicted in Figure 4. For preoperative patients, fasting glucose averaged 211 ± 27 mg/dL, and peak values were 434 ± 41 mg/dL. Mean fasting insulin value in the preoperative patients was 23 ± 4 μU/mL, which decreased slightly during the challenge and most likely reflects exogenous insulin. After operation, the sys-

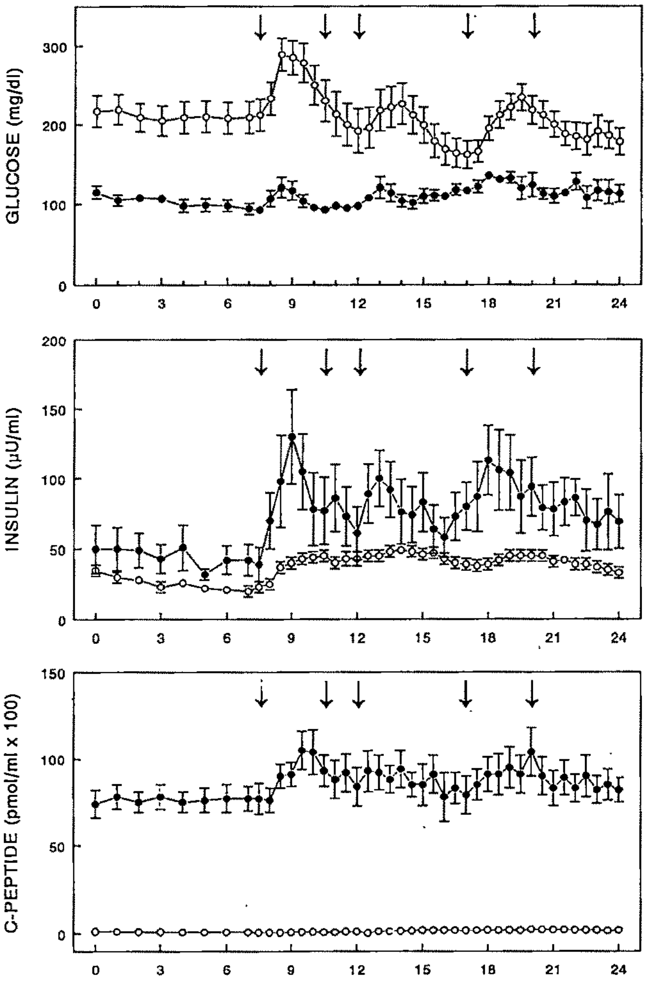

FIG. 3. Twenty-four-hour metabolic profile. Preoperative patient (n = 12) glucose, insulin, and C-peptide values at 1-hour intervals (O) are compared with postoperative values (●) of patients who received successful pancreas transplants. A basal and meal-stimulated hyperinsulinemia is apparent. Arrows denote meal or snack. Data are discussed further in the text.

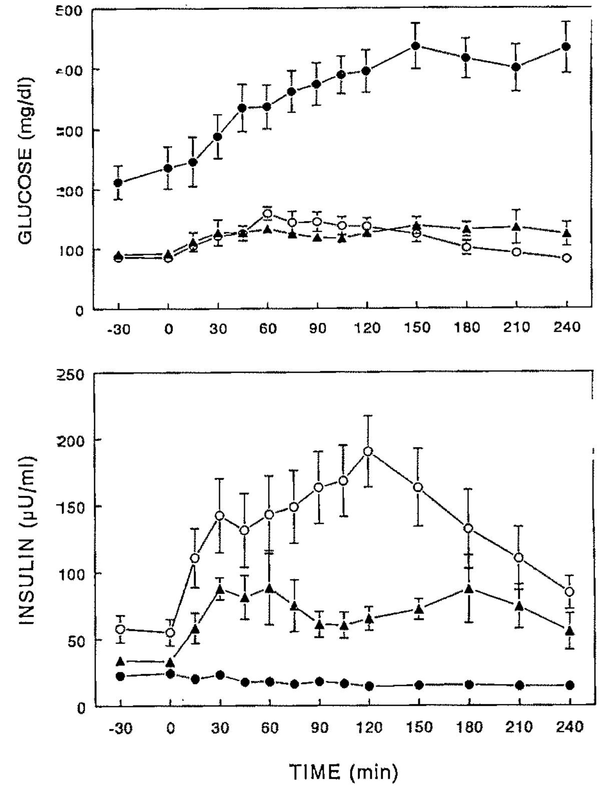

FIG. 4. Oral glucose tolerance test. Serum glucose and insulin levels (mean ± SEM) during a standard 100-g oral glucose challenge are shown for all preoperative patients (●). The postoperative patient values are divided into the systemically drained pancreatic grafts (O) and the portal drainage group (▲). The systemic drainage group shows a greater basal and meal-stimulated hyperinsulinemia after operation than the portal drainage group.

temically drained group had fasting glucose and insulin values of 87 ± 7 mg/dL and 56 ± 10 μU/mL, respectively, which peaked to a glucose level of 151 ± 11 mg/dL and an insulin level of 190 ± 26 μU/mL with stimulation. The portal drainage group demonstrated fasting glucose and insulin values of 91 ± 5 mg/dL and 34 ± 1 μU/mL, respectively, which peaked to 135 ± 28 mg/dL for glucose, and for insulin, 88 ± 27 μU/mL.

Figure 5 illustrates the integrated glucose response values after an oral glucose challenge for all preoperative patients *versus* all postoperative patients *versus* the systemically drained postoperative patients *versus* the portal drained postoperative patients. Successful pancreatic transplantation statistically lowers the integrated glucose response, yet none of the three transplant groups differ from the other postoperative groups. Figure 5 demonstrates the integrated insulin response for the same four groups. Systemic drainage of the pancreatic venous effluent results in a statistically significant increase in the integrated insulin response compared with the preoperative patients (19.4 ± 4 *versus* 127 ± 21 μU/mL/min). Portal drainage lowers the integrated insulin value to a level that is both statistically elevated from preoperative and decreased from systemically drained transplants (68 ± 7 μU/mL/min).

Preoperative and postoperative HbA1C values were also compared. The mean value dropped from 11.2 ± 3.3% to 5.1 ± 0.8% after successful pancreatic transplantation for the entire group. The mean preoperative serum creatinine was 5.4 ± 1 mg/dL, whereas the postoperative mean was 1.4 ± 0.1 mg/dL.

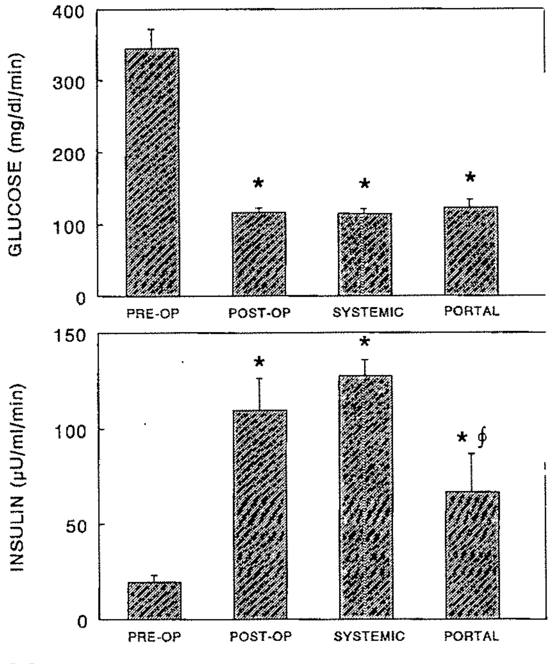

FIG. 5. Integrated response to oral glucose challenge. The integrated responses (area under the curve) of glucose and insulin to a standard 100-g oral glucose challenge. The results (mean ± SEM) are presented for patients before and after operation, with the latter group subdivided into portal *vs.* systemic drainage of the pancreatic graft. *$p < 0.05$ *vs.* preoperative value. § $p < 0.05$ *vs.* systemic.

Discussion

Pancreas transplantation has evolved dramatically since the first pancreas performed by Kelly and Lillehei at the University of Minnesota in 1966. The patient and graft survival has continued to improve over the years, with an average 1-year patient survival in the United States of 92% and an average pancreas graft survival of 72%.[1] Additionally, new techniques have been developed to decrease complications and enhance the ability to monitor rejection. It has become apparent that patient and graft survival are improved when a simultaneous pancreas–kidney transplant is performed.[16] This series, although small, demonstrates comparable survival statistics.

Survival

Our overall patient survival and 1-year patient survival is 95%. Other series report that most deaths are related to cardiac complications.[17] Pancreatic graft survival of 81% in our series is also comparable with other reported survival rates.[1,16–18] Three grafts were lost within the first 2 months, which all could be associated with technical errors, which included a harvest/perfusion injury, a ductal obstruction, and one episode of thrombosis, yielding a thrombosis rate of 4.7%, which is lower than other reported series.[19] No form of anticoagulation, heparin or low-molecular-weight dextran, is routinely used in our patients. Only one pancreatic graft was lost to rejection on postoperative day 449. This latter case serves as a reminder that although the kidney is an excellent monitor for rejection, with elevation of serum creatinine acting as a harbinger of pancreas rejection, a discontiguous rejection episode may occur. Elevation of serum glucose, which is a late finding, may be the only indication of this type of rejection because urinary amylase is usually not routinely monitored on an outpatient basis. This patient was especially interesting because he was the patient who underwent retransplantation of his pancreatic graft, so his functioning kidney and his functioning pancreas were immunologically different.

The reason for better results with simultaneous pancreas–kidney transplantation rather than sequential kidney–pancreas transplantation or pancreas alone remain largely unknown. Some speculate that the kidney plays a cytoprotective role. In our small series, we have three pancreas transplants alone and one performed 4 years after a living related donor renal transplant. All four of these pancreatic grafts functioned immediately and the patients have been insulin free since that time. This is in contrast to several studies that report an approximately 50% survival of pancreas transplants alone.[16,18,20,21] The reason for this difference is unclear. The long-term outcome of these patients as well as that of additional patients in this category require further evaluation.

Pancreatic grafts obtained from multiorgan donors, including liver donors, does not seem to adversely effect survival of pancreas grafts. We advocate the use of both organs whenever possible at a time in which organ shortage is currently a major impediment to transplantation. Additionally, University of Wisconsin solution remains the preservation solution of choice. Our results indicating a statistically significant difference in graft success with shorter ischemic time as opposed to graft failures with longer ischemic time differ somewhat from other studies that have shown no difference in survival with prolonged ischemic time.[18] Because only three grafts in our series failed in the first year, the association of prolonged ischemia and graft failure may be a reflection of a small series, and further evaluation with more patients would be beneficial. Currently we favor expeditious reimplantation. No additional factors could be isolated in our series that adversely affected graft survival.

Post-transplant Complications

Surgical and infectious complications remain an important contributor to morbidity and mortality rates in all transplant populations. Our series reveals an acceptable complication rate for both surgical problems and infectious complications. When the complications are divided into the technical success group and the technical failure group, it is very apparent that most serious complications occur in the latter group. The patients who have one complication are more likely to have a series of complications. The incidence of both surgical and infectious complications in the graft failure group was three to four times that of the graft success group. The nature of the infectious complications in the technical failure group tends to be more serious, with pathogenic bacteria isolated including *Pseudomonas aeruginosa, Citrobacter freundii,* and *Enterobacter.* These organisms reflect the severity of their illness induced by multiple complications associated with a graft failure. Our series reports a high incidence of CMV infections. The CMV infections did occur in the expected time frame of 4 to 6 weeks after transplantation. Herpes simplex virus also was isolated five times and required therapy but did not cause any serious infections and were usually treated on an outpatient basis.

The current preference for pancreatic exocrine drainage is through the urinary bladder. The incidence of bladder leaks and complications has decreased with the increased use of duodenal segment rather than a duodenal button for the duodenoneocystostomy anastomosis.[18] Problems arise with metabolic acidosis in some patients secondary to the urinary bicarbonate loss, however. Thus, a technique that places exocrine secretions into the gastrointestinal tract may be a reasonable alternative.

Post-transplant Glucoregulation

Surgical alterations of the pancreas necessary for transplantation result in changes in insulin delivery that allow for examination of carbohydrate metabolism in both the diabetic and the normal state. Metabolic studies of pancreas transplant recipients during the early successful period of pancreas transplants suggested the possibility of increased fasting and meal-challenged insulin levels.[22] After documentation of increased success rates, further physiologic evaluation demonstrated that elevated insulin levels were associated with the techniques of transplantation, which employed systemic release of insulin in humans as well as animal models.[23–26]

The reasons for hyperinsulinemia after transplantation of the pancreas are not entirely clear. Surgical alterations necessary to perform the transplantation, including denervation, which may release an inhibitory effect, or simply the systemic release of insulin, which bypasses a "first-pass" hepatic extraction, may be an explanation for post-transplant elevations in insulin levels. Another possibility may be that the immunosuppressive agent, cyclosporine, might affect either the beta-cell release of insulin or may modify systemic sensitivity in a fashion that might lead to a stimulus for higher peripheral levels of insulin to "normalize" glucoregulation.[27,28] The association of hyperinsulinemia with other long-term consequences has been reported. Insulin therapy, and perhaps hyperinsulinemia, *per se,* have been suggested to be associated with atherosclerosis and vascular endothelial damage.[29–32] In fact, a recent study in animals demonstrated increased triglyceride content in skeletal muscles and arterial wall samples after systemically drained pancreas transplantation, which resulted in elevated basal and challenged insulin values.[33]

We have recently adopted a technique of pancreas transplantation that employs a venous anastomosis into the portal system through the proximal splenic vein. This technique necessitates enteric drainage of the exocrine pancreas and therefore the loss of the capability of monitoring graft rejection by urinary amylase levels, which popularized the bladder drainage technique. We believe, however, that portal drainage of the graft results in more physiologic insulin values, especially after glucose stimulation. Interestingly, basal insulin is still high (25 to 35 μU/mL), albeit lower than the systemically drained transplants. Whether or not lowered insulin values have an impact on long-term complications requires further evaluation. Initial reports in animals, however, have documented that animals with portal drained insulin sources have decreased peripheral insulin levels and decreased muscle and arterial triglyceride levels compared with animals with systemically drained insulin grafts.[33] By comparing the data in Figures 5, it is intriguing to note that high or low insulin values have no effect on the integrated glucose values, a finding we have seen in animal models.[26] This suggests that absolute insulin values in the periphery may not be the important glucoregulatory event. It may be that another aspect of insulin secretion, perhaps pulsatile secretion patterns, which may have a greater significance than previously thought.

In conclusion, our initial experience corroborates the work of others that pancreas transplantation has proven to be an acceptable therapeutic option for type I diabetes mellitus. The patient and graft survival rates continue to improve. New techniques and modifications of existing procedures continue to evolve in an attempt to decrease morbidity and mortality rates associated with pancreas transplantation as well as to attempt to minimize metabolic alterations from normal physiologic mechanisms.

Acknowledgments

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DISCUSSION

JAMES C. THOMPSON (Galveston, Texas): This is really a spiffy paper, and I am honored to be asked to talk about it. Obviously, a whole-organ transplantation of the pancreas is not the answer to diabetes, because in the process of doing it, you stuff a whole lot of exocrine cells into the body that can only cause trouble. They have no way of doing any good; they can only do bad, and they all end up going bad at one time or another. In Galveston we have had experience for a little more than 3 years. We have done a few more than 30. And what you do when you get in the pancreas transplant business is you never get rid of the patients. They are always hanging around, do not get too far away, and they come back in frequently, and you get to know all of them and their children and their families by their first names. But it is a wonderful treatment. It is not perfect, but it is wonderful. And I think that what we see here is really probably about as good as we are going to get with whole-organ transplantation.

This is a very nice manuscript, and I learned a lot from it. First of all, it has a nice review of the literature. In 25 years, I am told that more than 1400 pancreas transplants have been done. One of the things I would like to ask the authors is whether provision of normal pancreatic insulin, that is, insulin not out of a bottle, halts or affects the lethal progression of obliterative vascular disease in the kidney, brain, retina, and heart. We are doing this on the assumption that it does. And Marshall Orloff, in a series of brilliant studies in diabetic mice, provided evidence that it does. We have now been doing this for 25 years. What is the evidence in humans? I am sure you know a lot about that.

I think everything in this paper is spiffy, and I really like that idea about putting the portal venous blood or the insulin venous blood—the pancreatic venous blood—into the portal vein. But what is really bad about hyperinsulinism? I mean, you talk about it, but is it really bad? Does anybody get into trouble with this hyperinsulinism who has their pancreas drained into the systemic venous system?

Also, you make a few side remarks in the manuscript about the problems of alkalosis when you put the drainage of the pancreas and duodenum into the bladder. What complications did you actually see of that metabolic alkalosis? And I guess the most important thing is what are you going to do in the future? Are you going to do all of these by draining them into the portal vein? Are there some that you cannot? Are there limitations to this? Is this something that everybody ought to be taking up? Now the University of Virginia at Charlottesville is known for many things. One of them is that they have a system of elegant studies of glucose clamp techniques to determine hepatic glucose metabolism, and they have been studying the effect of insulin and glucagon and GIP. And they showed us some studies in preoperative patients. Now I know you have done these in these people, that you have drained the pancreas into the portal vein. And how do they differ? How do these glucose clamp studies differ in this small subset of your three patients from those in whom you drained the pancreatic vein into the systemic venous system?

Thanks a lot.

DR. WALLACE P. RITCHIE, JR. (Philadelphia, Pennsylvania): Dr. Thompson is always a very difficult act to follow, particularly when he asks the only question I could think of about this paper.

I would like to congratulate Dr. Hanks on what appears to be an excellent series with marvelous results and quite comparable to larger series from people who have been in the business for a long time. And I would like to thank him for the opportunity to review the manuscript and for asking me to comment on it very briefly. I am not entirely sure why he did this, except for the fact that he does have a deep sense of history, which is genetic, and he does know that I have scrubbed on one pancreas transplant procedure in my entire life. But it did happen to be the very first one ever done in humans, and that was done at the University of Minnesota in the mid-1960s by Drs. William Kelly and Richard Lillehei. I was also, at least in part, responsible for the care of the patient after the transplant, which was done very much, John, as I recall, in the manner in which you have depicted your last three patients of your own. As the euphemism has it, that was a very stormy postoperative course—very stormy. I think a lot of progress has been made, from one sort of sitting on the sidelines. And, at least to my untutored eye, I think treating the pancreatic graft, as Dr. Sollinger and Dr. Belzer have shown us, in the same technical way relative to exocrine secretion in vascular anastomoses, as one would treat a renal allograft, has represented a major step forward.

So what Dr. Hanks is now suggesting is that perhaps transplant surgeons may have been too cavalier—and that is the appropriate term in Dr. Hanks' case—about the consequences of systemic hyperinsulinemia, which current techniques of graft implantation make inevitable. Perhaps we will see impaired hepatic glucose metabolism, and that is why the question about the clamp that Dr. Thompson raised is an important one. Perhaps we will see beta-cell exhaustion. Perhaps we will even see acceleration of atherosclerosis. The method he proposes for delivering insulin to the portal circulation may, in fact, ameliorate the supposed problems. But it does appear to be technically rather demanding, very similar to what I saw back in the 1960s. So the real issue here is what is the risk-benefit ratio. My question for Dr. Hanks then is, how real are these concerns? I would simply point out that an article recently appeared in the *New England Journal of Medicine* just last month in which glucose and insulin metabolism were studied in three groups of patients, much like those that John showed us in his glucose clamp study. Pancreas-kidney transplants were performed in the standard way, in diabetic recipients, none of them required insulin, all were euglycemic; nondiabetic renal transplant recipients were used as controls for immunosuppression, as well as normal subjects. And although the first group did have, as expected higher fasting and postprandial insulin levels, there were absolutely no differences between any of the groups under the same circumstances with respect to glucose concentration, plasma glucagon levels, the rate of appearance or disappearance of ingested glucose in the systemic circulation, hepatic glucose release, or the rate of incorporation of CO_2 into glucose. In other words, there was grossly normal glucose metabolism despite systemic hyperinsulinemia.

So I think the real important question, John, is this: What is the real case for portalization of the venous effluent from pancreatic allografts? I enjoyed the paper very much indeed and appreciate the opportunity to discuss it.

DR. F. O. BELZER (Madison, Wisconsin): I also enjoyed the paper, but I would just have a word of caution. First, this technique was actually first described by Roy Calne about 4 years ago and subsequently has been abandoned. The only difference was that he used the splenic artery and splenic vein with exocrine drainage into the stomach.

We have also done approximately 10 enteric anastomoses. If something goes wrong with the bladder anastomosis, you end up with a live patient and usually a still functioning graft. If you get a complication with an enteric anastomosis, you frequently end up with graft loss and sometimes with patient loss, unless you use the very elaborate technique that is used in Stockholm with long-term external drainage of the pancreatic duct itself.

As there really is no evidence that hyperinsulinism is detrimental, why use an operation that is more dangerous than the bladder technique? Interestingly enough, if you do the bladder technique and 6 or 10 months later you convert it to intestinal drainage, the complications are much less because the exocrine function has usually been more or less exhausted, and your vascular anastomosis is mature. In my opinion, the intestinal anastomosis in pancreas transplantation is more hazardous, and I would just warn you that you are going to see complications that may be serious.

DR. LYNN ROSENLOF (Closing discussion): I would like to thank Dr. Britt and Dr. Jones. I also would like to thank Dr. Thompson and Dr. Ritchie for the fine and complimentary comments and Dr. Belzer for the well-thought-out and cautious comments, because these are in fact very true points, and we do need to proceed with caution. This new technique is not necessarily the exact answer to all the problems that we have. We are fortunate that, in the three patients on which we have done portal drainage, there have been no problems with enteric anastomotic leaks. We also have had very limited—actually no—bladder leaks when we did the ureteroneocystostomies. Variations of this technique have been introduced in the past, and it has been abandoned, but most of those were gastroenteric anastomoses. We agree that the enteric anastomosis is the Achilles heel of this procedure. Several technical factors contribute to the paucity of problems that have been observed. First, the side-to-side duodenojejunostomy is made with the EEA stapler. By entering the long fourth portion of the donor duodenum, precision is maximized. Secondly, instillation of intraduodenal antibiotics has markedly reduced microbial inoculum from the donor and recipient. Thirdly, preservation of the pancreas is better than ever, in large part due to the solution that carries your name, and donor duodenal distension is minimized. Lastly, the anastomosis is made distal enough on the jejunum so that if a leak occurred, removal of the pancreas would allow for reconstitution of the small bowel, and outstanding success has been accomplished with the systemic drainage. But we still do see the issue with systemic hyperinsulinemia. In both animal and human studies, it has been clearly documented that the systemic hyperinsulinemia does exist; however, its detrimental long-term effects have not been well documented. Current studies have shown that systemic hyperinsulinemia may lead to increased atherogenesis and progression of peripheral vascular disease in some of these patients; however, other studies have not been quite as able to confirm these findings.

There is a recent study in a canine model that looked at peripheral triglyceride levels in the vascular arterial walls and in the muscles. The study showed increased concentrations of triglycerides in a canine model where they induced systemic hyperinsulinemia. Again, whether this long-term systemic hyperinsulinemia does cause these detrimental effects and increased atherogenesis remains to be seen, and these long-term studies need to be further carried out.

Additionally, in our patients who have undergone systemic drainage—and we have documented the systemic hyperinsulinemia—most of their metabolic studies were done in approximately 12 months after operation. Because we are a relatively new program, we are still studying these patients, and it will be interesting to see whether this systemic hyperinsulinemia persists over a long period. There have not been any long-term studies to show whether this systemic hyperinsulinemia persists. It appears that draining the pancreatic venous effluent into the portal system seems to be more physiologic, but it still does not answer all of the questions. We have portally drained three patients, and we still see a relative basal hyperinsulinemia.

Dr. Thompson has made some very kind comments, which we appreciate. We are in the process of bringing them back into the Clinical Research Center.

Dr. Thompson also referred to whether systemic or portal drainage of successful pancreas transplantation is able to halt the progression of secondary diabetic complications such as progression of peripheral vascular disease and retinopathy. This has been studied over a long period, and in reviewing the literature it remains controversial. Some studies show that there is some improvement, but longitudinal studies are needed for confirmation.

I would like to say thank you for all the kind comments, and I especially appreciate the cautious words of Dr. Belzer, because this is a very new technique, and I do not think it will be the complete answer. We feel it certainly offers an alternative technique to deal with some of the issues regarding the systemic hyperinsulinemia that has unknown detrimental effects, as well as some of the metabolic consequences of the bladder drainage technique. We have had several patients who have had significant metabolic acidosis develop from the pancreatic exocrine secretion into the bladder. In fact, last week we had to take one patient who is now approximately 3 years out from his pancreas transplant back to the operating room and convert him to enteric drainage. And Dr. Belzer's comments with regard to late conversion of enteric drainage also may be a reasonable alternative. I would like to thank the Association for the opportunity to discuss this paper.

The Interrelation Between Sclerosing Cholangitis and Ulcerative Colitis in Patients Undergoing Liver Transplantation

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Thirty-six patients underwent orthotopic liver transplantation (OLT) for primary sclerosing cholangitis under cyclosporine, azathioprine, and steroid immunosuppression. Of these patients, 29 suffered from chronic ulcerative colitis. The purpose of this study is to determine (1) whether replacement of the diseased liver and the altered immunocompetence suppresses the manifestation of chronic ulcerative colitis, and (2) if active colonic disease alters allograft function. Thirty of 36 patients survived OLT. After OLT, seven of 14 patients with symptomatic colon disease at the time of transplantation continue to suffer from active chronic ulcerative colitis, and three of 13 who were asymptomatic developed clinically active disease. Intractable colonic disease was the indication for post-OLT proctocolectomy in three patients, and one refused an indicated colectomy. Despite the long duration of the disease, none developed colonic malignancy. Long-term graft assessment showed good hepatocyte synthetic function in patients suffering from either active or inactive disease. Liver alkaline phosphatase, however, was significantly higher in patients suffering from active colonic disease. Furthermore, the alkaline phosphatase in symptomatic patients was higher than that seen in a matched cohort undergoing OLT for chronic active hepatitis or primary biliary cirrhosis. These results suggest that (1) liver replacement and immunosuppression in patients suffering from sclerosing cholangitis and ulcerative colitis do not alter the course of the colon disease, and (2) active chronic ulcerative colitis does not adversely affect allograft function, although elevation of alkaline phosphatase may be the harbinger of recurrence over the long term.

PRIMARY SCLEROSING CHOLANGITIS (PSC) is an uncommon disease that causes an inflammatory reaction resulting in fibrosis of the biliary ductal system, and the subsequent development of cirrhosis. The causative factors leading to the destruction of both intrahepatic and extrahepatic bile ducts are yet to be determined. Possible mechanisms include immunologic disorders, bile and biliary mucosal abnormality, or infectious agents.[1] Almost 70% of the patients with PSC are found to suffer from inflammatory bowel diseases, mainly chronic ulcerative colitis (CUC).[2] Despite the frequent association of PSC and inflammatory bowel disease, however, neither a common pathogenesis nor a direct cause–effect relationship between the two conditions has been identified. The controversy surrounding the role of the colon disease in the development of PSC is fueled by some reports that indicate that early proctocolectomy may arrest or prevent the development of end-stage PSC.[3,4] Conversely, a large series from the Mayo Clinic indicates that proctocolectomy had no influence on the natural progression of PSC.[5] This latter study is hindered by the fact that at the time of the colon removal, PSC was already established. The presence of normal colonic mucosa in advanced PSC was used also to argue against an association between the colon and the pathogenesis of the liver disease. In this report, we studied the fate of the liver graft, as well as the activity of the colonic disease after orthotopic liver transplantation (OLT). The purpose of this study was to determine: (1) the impact of active *versus* inactive colonic disease on the function and survival of the normal allograft, and to document the recurrence of PSC (2) The effect of a normal liver graft and active immunosuppression on the post-transplant activity of CUC. (3). Whether CUC will develop in transplanted patients who were free of colonic disease before their OLT.

Methods

The charts of 400 consecutive adult patients undergoing OLT at University of California, Los Angeles between

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1985 and 1990 were examined. Thirty-six patients were identified as suffering from end-stage liver disease secondary to PSC. There were 22 men and 14 women, with a mean age of 42.7 years (standard deviation ± 9.2). The following criteria were used to establish the diagnosis of end-stage liver disease secondary to PSC: (1) Clinical signs and symptoms of jaundice, pruritus, cholangitis, and complications of portal hypertension (2) endoscopic retrograde cholangiopancreatography or transhepatic cholangiography that demonstrated the typical findings of multiple strictures and dilatations of the intrahepatic and extrahepatic biliary ducts. (3) Preoperative liver biopsy showing histologic findings of periportal fibrosis and advanced cirrhosis. These findings were confirmed by microscopic examination of the diseased liver after OLT. Patients who were diagnosed before operation as suffering from cholangiocarcinoma associated with PSC were excluded from analysis.

All patients who had been evaluated for OLT underwent a preoperative assessment of their colonic disease. History of active CUC, abdominal pain, diarrhea or bloody diarrhea at any time prior to the evaluation mandated preoperative colonoscopy and biopsy to rule out malignancy. Exceptions were patients who underwent proctocolectomy and did not report any symptoms of bowel disease after the operation.

Patients undergoing OLT and suffering from CUC were separated into four groups, based on the presence of clinical symptoms or colonoscopic findings. Group I patients suffered from active clinical and colonoscopic disease, group II had quiescent clinical but colonoscopic signs and biopsy evidence of mucosal inflammation, group III had inactive clinical disease with normal colonoscopic findings, and group IV underwent total proctocolectomy before OLT. The preoperative status of the bowel disease was compared with the most recent, post-transplant clinical symptoms and colonoscopic findings.

Orthotopic liver transplantation was performed as previously described. The only modification was resection of the entire common bile duct to the pancreas, and reconstruction of the biliary system with a Roux-en-y choledochojejunostomy. The cut surface of the bile duct was sent for frozen section in cases suspected of cholangiocarcinoma; however, tumor was not found in any of the patients.

Post-transplant maintenance immunosuppression in this group included prednisone 5 to 15 mg/day, azathioprine 1 mg/kg/day, oral cyclosporine (adjusted to obtain whole blood high-pressure liquid chromatography levels of 150 to 300 ng/mL), or FK 506 (adjusted to plasma levels of 0.5 to 2.0 ng/mL). Long-term post-transplant graft function was followed by routine liver function tests at 6-month intervals. The mean follow-up after OLT in this group is 29.5 months (standard deviation ± 17.6).

After OLT, all patients were routinely observed for the development of colonic and liver dysfunction. Surveillance colonoscopy and biopsy and liver biopsy were performed when indicated. Percutaneous transhepatic cholangiography was used to confirm the existence of intrahepatic or extrahepatic bile duct pathology if clinically suspected. Routine liver tests, at 6-month intervals included: albumin, prothrombin time (synthetic function), serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, and total and direct bilirubin.

Statistical Analysis

The data are expressed as mean and standard deviation. Comparison between groups were performed by using the standard un-paired Student t test. All statistical analysis was performed using Statview 512 + TM (Interactive Statistics and Graphics package, Abacus Concepts, Inc).

Results

Patient Outcome

The actuarial 1- and 5-year survival rate for patients undergoing liver transplantation for PSC at University of California, Los Angeles, is 80% and 76%. Twenty-nine of 36 patients are alive and back to a normal activity. The early (3-month) postoperative mortality rate was 17% (6/36), and was related to graft failure (rejection 1/6) or systemic infection (5/6). Late follow-up disclosed only one death due to recurrent cholangiocarcinoma (not diagnosed before operation).

Preoperative Liver Disease

Pretransplant manifestation of end-stage liver disease and the indications for transplantation are summarized in Table 1. Common symptoms were severe fatigue, inability to maintain normal routine activities, and significant weight loss. Other findings included: portal hyper-

TABLE 1. *Indications for Orthotopic Liver Transplantation in End-stage Primary Sclerosing Cholangitis*

Indication	No. of Patients
Life style	
Decreased activity	36 (100%)
Chronic fatigue	36 (100%)
Portal hypertension	
UGI bleeding	10/36 (28%)
Ascites	21/36 (58%)
Recurrent encephalopathy	9/36 (25%)
Hyperbilirubinemia	36/36 (100%) (18.8 ± 9.1)
Poor synthetic function	
PT > 3 sec	11/36 (31%)
Albumin < 3 g/dL	17/36 (47%)

tension and recurrent upper gastrointestinal bleeding (10/36), ascites (21/36), and recurrent episodes of hepatic encephalopathy (9/36). Preoperative laboratory findings were hyperbilirubinemia (mean, 18.8 mg/dL, standard deviation = 9.1), and poor hepatic synthetic function (hypoalbuminemia < 3.0 g/L in 17/36, prothrombin time > 3 seconds than control in 11/36). The mean time between acceptance as a transplant candidate to transplantation was 6 weeks, and we did not observe significant deterioration of the liver disease during this period.

Incidental cholangiocarcinoma was found during hepatectomy in two patients; both had small tumors (less than 2 cm in diameter) at the hilum of the liver. These patients underwent uneventful OLT and the resected margins appeared to be free of tumor. However, one died of recurrent cholangiocarcinoma 20 months after transplantation, the other is free of disease 4 years after surgery.

Post-transplant Graft Function

Six patients were admitted for episodes of biopsy-proven acute rejection within 3 to 12 months of OLT. They responded well to the administration of high-dose methylprednisolone, or OKT3 monoclonal antibody. Chronic rejection was recognized in two patients; both had an extensive workup that ruled out hepatitis, and vascular or biliary tract pathology. The biopsy findings were significant for chronic periportal inflammation with mononuclear infiltrate, lobular hepatocyte necrosis, and vanishing bile ducts. These two patients did not report post-transplant symptoms of active CUC.

Delayed strictures of the biliary enteric anastomosis occurred in two patients; the presenting symptom was septic cholangitis and rising bilirubin. Percutaneous transhepatic cholangiogram demonstrated the anastomotic stricture;, both responded well to dilatation and short-term percutaneous transhepatic stent.

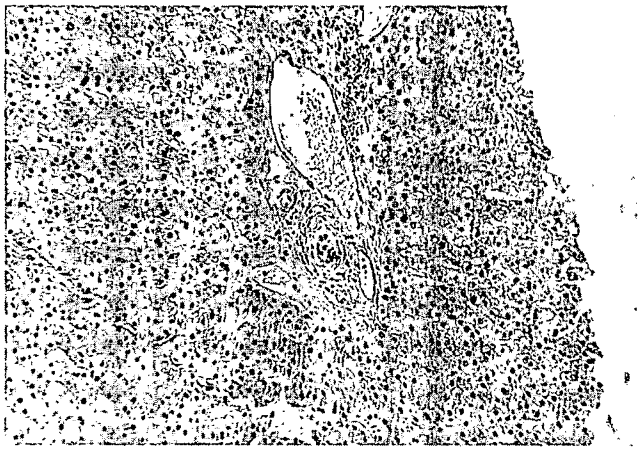

FIG. 1. Liver biopsy specimen 14 months after liver transplantation shows bile duct with periductal fibrosis.

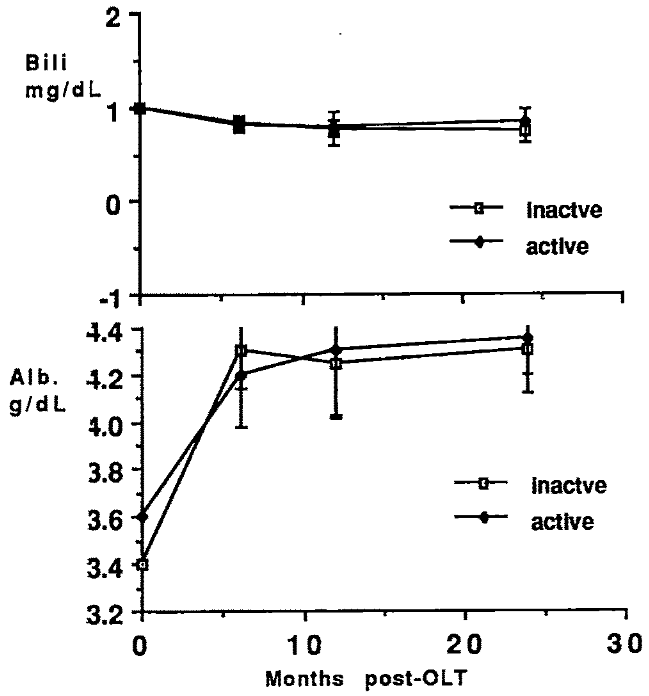

FIG. 2. Post-transplant synthetic graft function (albumin) or total bilirubin was not different between patients with inactive and those with active colonic disease.

Possible recurrent sclerosing cholangitis was recognized in only one case. This patient was treated for two episodes of acute rejection within the first 6 weeks after transplantation, because then he did not suffer from elevated transaminases or biopsy-proven rejection. Doppler sonography scan in this patient demonstrated arterial blood supply to the liver graft. The first abnormal finding, 6 months after transplantation, was a persistently elevated alkaline phosphatase, with levels of 680 ± U/L. Multiple liver biopsies showed periductal fibrosis, similar to that seen in early sclerosing cholangitis (Fig. 1). Transhepatic cholangiogram demonstrated the narrowing of the intrahepatic bile ducts with distal dilatation. This patient continued to suffer from intractable active CUC, and recently underwent total proctocolectomy. Current liver tests demonstrate persistant elevation of alkaline phosphatase; however, it is too early to determine the effect of proctocolectomy on the liver graft.

Hepatic transaminases, bilirubin, and albumin are within normal range in all surviving patients (Fig. 2). Twelve months after OLT, however, eight patients with active ulcerative colitis had higher levels of alkaline phosphatase when compared with 21 with inactive disease, or with those who had proctocolectomy before OLT (Fig. 3) (226.5, standard error 111 *versus* 112.2, standard error 12.1, p = 0.12), or to a matched cohort of PBC and chronic active hepatitis patients (Fig. 4). The difference in alkaline phosphatase between the two groups reached statistical

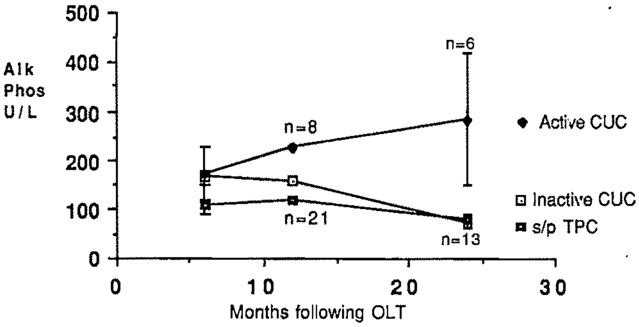

FIG. 3. Post-transplant follow-up of alkaline phosphatase in patients with or without colonic symptoms shows significant difference at 24 months (p < 0.017).

significance at 24 months, when six patients with active CUC were compared with 13 patients with inactive disease (285.6, standard error 134.7 *versus* 73, standard error 6.5, $p = 0.017$). Despite the significantly elevated alkaline phosphatase and the presence of active colonic disease, these patients continue to do well, and do not have any clinical or biochemical evidence of liver dysfunction.

Preoperative Bowel Disease

The existence of clinical and colonoscopy-proven inflammatory bowel disease/CUC was known in 29 of 36 patients (80%) (Fig. 5). There were no cases of Crohn's disease of the large or small bowel in this group. The mean duration of CUC before OLT was 17.4 years (standard deviation ± 10.2).

The bowel disease was found to be clinically symptomatic in 12 of 29 patients who were treated with either azulfidine or steroids. These patients complained of abdominal pain, multiple soft bowel movements, and intermittent bloody diarrhea. Colonoscopic findings of active inflammation were seen in 14 patients (12/14 with clinical symptoms). Eleven of 29 had no symptoms related to bowel disease (11/29), and normal or quiescent disease by colonoscopy. Adenocarcinoma *in situ* was seen in one patient who underwent abdominal colectomy at the time of transplantation. Four of 29 patients underwent total proctocolectomy, before the development of end-stage PSC. The indications for bowel resection was chronic disease with recurrent acute exacerbations, refractory to medical therapy. Only one patient was found to suffer from Dukes' B adenocarcinoma in the left colon; this patient underwent total abdominal colectomy and ilioproctostomy 6 years before his transplant.

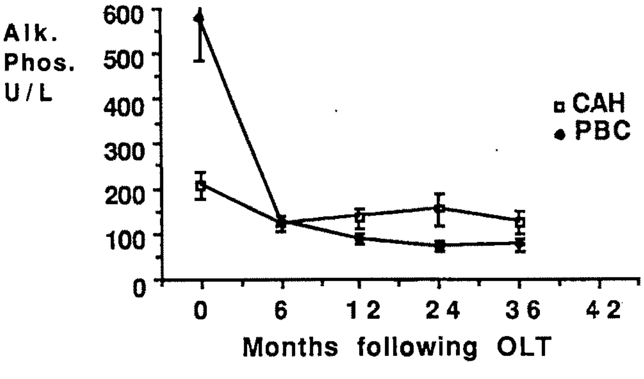

FIG. 4. Alkaline phosphatase levels remain stable 6 to 36 months after OLT for PBC or CAH. These levels were lower than those found in patients who underwent transplantation for PSC and who had active CUC.

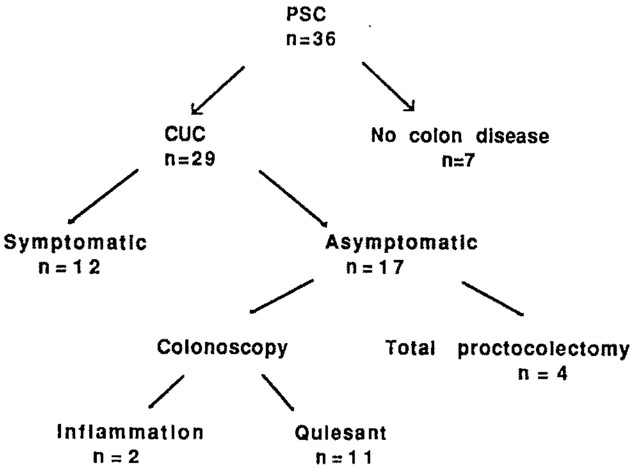

FIG. 5. The existence of chronic ulcerative colitis was documented in 29 of 36 patients who underwent OLT for end-stage PSC. However, only 12 patients had active colonic disease.

Postoperative Bowel Disease

Changes in the post-transplant activity of the colonic disease are demonstrated in Table 2.

Group I

Preoperative clinical and colonoscopic active disease was found in 12 patients. One patient in this group underwent total abdominal colectomy at the time of transplantation. Post-transplant active CUC as reported by

TABLE 2. *Alteration in the Activity of Chronic Ulcerative Colitis After Orthotopic Liver Transplantation*

	Post-transplant Activity			
	A	B	C	D
Pretransplant activity				
A n = 12	7	3	2	
B n = 2	1	1		
C n = 11	3		8	
D n = 4				4
Total n = 29	11	4	10	4

A, active clinical disease with biopsy-proven mucosal inflammation; B, asymptomatic, biopsy-proven mucosal inflammation; C, asymptomatic, no evidence of mucosal inflammation; D, S/P proctocolectomy.

seven of 12 patients who continue to suffer from mild diarrhea and colonoscopy confirmed the presence of active inflammation. Surveillance colonoscopy showed active inflammation in three patients who were clinically asymptomatic. Thus, only 1 of 12 patients suffering from pretransplant active CUC is free of symptoms, and has normal colonic mucosa. Within the symptomatic group, severe incapacitating post-transplant colitis required total proctocolectomy in two patients. Both were advised not to have ileoanal pull-through or reconstruction of a continent pouch, because of concern about postoperative bowel complications in the immunosuppressed patient. One other patient developed acute cecal perforation and underwent emergency abdominal colectomy; the pathology findings demonstrated diffuse severe mucosal disease. Proctocolectomy was refused by a patient with severe clinical symptoms, and mucosal biopsies demonstrating areas of severe atypia and premalignant changes. The transplanted patients were able to tolerate large bowel resections without developing significant abdominal- or liver graft-related complications. There were no postoperative abdominal or liver-related complications in this group.

Group II

Preoperative colonoscopic findings of active disease with no clinical symptoms was seen in two patients. After OLT, one patient developed clinically active disease; the other patient does not report any gastrointestinal symptoms, but continues to have colonoscopic findings of mild mucosal inflammation.

Group III

Eleven patients did not report any pretransplant symptoms of CUC, and had no evidence of colonic mucosal inflammation on surveillance colonoscopy. Three patients in this group developed clinical symptoms and colonoscopy-proven CUC 1 to 3 years after transplantation. The others (8/11) do not report any colonic symptoms, and are not followed by routine colonoscopy.

Group IV

Four patients who have had proctocolectomy before transplantation, have no gastrointestinal complaints after OLT.

Routine follow-up, including surveillance colonoscopy, did not detect any evidence for post-transplant colonic or extracolonic malignancy in patients suffering from long-standing CUC.

Discussion

The frequent association between ulcerative colitis and primary sclerosing cholangitis, and the higher incidence of PSC among patients suffering from inflammatory bowel disease, suggest a linkage between the two. An attempt to directly implicate active colonic disease in the induction and progression of the liver disease, however, has met with some difficulties.[2,6,7] The possible role of colonic toxins and portal colonic pathogens could not explain the finding of PSC in patients without clinical symptoms or colonoscopic findings of mucosal pathology. Furthermore, total proctocolectomy in patients with active CUC did not arrest the progression of PSC.[5]

A major critique of reports proposing that proctocolectomy does not halt the progression of PSC is that the patients studied already manifested severe ongoing liver disease, and a stimulated immune system that was operative may continue to destroy the biliary ducts despite removal of the initiating factor (colon). Previous studies have emphasized the involvement of the immune system in PSC, the presence of circulating immune complexes, enhanced autoreactivity of CD8+ lymphocytes against class II antigens, and the involvement of T cells in the disruption of biliary epithelium.[8,9] More recent reports demonstrate the presence of shared antigenic epitopes on colonic and biliary epithelia, as well as antineutrophil cytoplasmic antibody in the serum of patients with both conditions.[10,11] Thus, such mechanisms may involve the continuous production of autoreactive antibodies against biliary epithelial antigens, even in the absence of the colon or rectum. Such phenomena were shown to exist for other autoimmune diseases.[12]

Orthotopic liver transplantation presents a unique opportunity to follow the fate of a normal liver graft and to correlate early cholangitic abnormalities with the presence or absence of active CUC. It should be emphasized, however, that the relatively short-term follow-up (median, 27 months) may not accurately reflect the incidence of recurrent PSC. Furthermore, the presence of ongoing chronic rejection may mimic the histological and biochemical findings seen in early sclerosing cholangitis.[13]

This study demonstrates that long-term graft survival and synthetic function are not affected, at 1 to 3 years' follow-up, by the activity of the colonic disease. In only one case were we able to document histologic and cholangiographic evidence of recurrent sclerosing cholangitis. Similar findings, with only one recurrent PSC, were reported in a series of 37 patients who were transplanted for end-stage PSC in the Pittsburgh experience.[13] A significant finding in our study is an elevation of alkaline phosphatase, at 12 and 24 months after transplantation, in patients suffering from active CUC. This is interesting in view of recent descriptions of asymptomatic elevation of alkaline phosphatase, which were reported in 20% of patients with ulcerative colitis. This was attributed to an ongoing pericholangitic inflammation around the bile ductules.[14,15] Although pericholangitis has been thought to be innocuous, more recent findings suggest that it may represent an early stage of sclerosing cholangitis.[16] An important differential diagnosis is ischemic cholangiopathy secondary to hepatic artery thrombosis or vascular rejection. Under such circumstances, there will be continuous destruction of the intrahepatic bile ducts, leading to the development of strictures and segmental ductal dilatation, and cholangiographic findings are similar to those described in PSC.[17] All our patients underwent Duplex scan, however, which demonstrated the hepatic artery to be open. In the absence of vascular complications, the findings of elevated alkaline phosphatase in patients with active CUC, may be attributed to early pericholangitis. This findings needs long-term follow-up to determine whether some of these patients will develop recurrent sclerosing cholangitis. The elevation of this enzyme in the presence of active CUC, however, and not in the presence of quiescent colonic disease or after colectomy, suggest some more direct association between the two.

The hypothesis of the role of active CUC in the development of sclerosing cholangitis may lead to the question of whether suppression of active colonic disease will be associated with normalization of the alkaline phosphatase, and prevent late recurrence of pericholangitis and PSC. Previous reports demonstrated the benefit of oral prednisone, as well as cyclosporine and azathioprine, in the control of periodic exacerbations of CUC.[18,19] This was not demonstrated in our series. Most of the patients who had preoperative active colon disease continued to suffer from similar symptoms, despite maintenance treatment with steroids, cyclosporine, and azathioprine. In addition, patients who had no clinical or colonoscopic evidence of CUC before OLT, given the time, developed active post-transplant colonic disease. These data suggest that the chronic use of immunosuppression, in the post-transplant period, does not alter the course of the colonic disease. Furthermore, the development of post-transplant ulcerative colitis in patients who had no evidence of this disease before transplantation suggests an even closer pathophysiologic relationship between PSC and CUC. The colonic disease eventually may be expressed in those whose death of end-stage liver disease is being prevented by OLT. Thus, colonic pathologies associated with post-transplant clinical CUC should be searched for inpatients with end-stage PSC but no prior evidence of CUC.

Our observations support the hypothesis of a similar pathophysiologic mechanism common to both PSC and CUC. There may be a differential target organ expression, however.. Replacement of the liver does not appear to alter the colonic disease despite the use of cytotoxic and immunosuppressive agents, and those patients should be monitored carefully. Although active colonic disease has not been demonstrated to cause development of recurrent PSC, the insidious rise of alkaline phosphatase seen in these patients may represent a harbinger for the development of recurrent PSC. Moreover, it may support the hypothesis that colonic factors are involved in the induction or propagation of the liver disease. Longer follow-up is needed to confirm these findings.

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DISCUSSION

DR. HENRY PITT (Baltimore, Maryland): My first question relates to how the diagnosis of ulcerative colitis was documented. Patients with sclerosing cholangitis often have diarrhea and sometimes have steatorrhea due, in part, to a deficiency of bile salts and, in some patients, to associated chronic pancreatitis. The 81% incidence of ulcerative colitis in your patients with sclerosing cholangitis is somewhat higher than in most series. You have provided information on colonoscopy and biopsy, but my question is whether patients who are clinically and biopsy negative really have ulcerative colitis?

My second question deals with the development of cholangiocarcinoma. In most series of patients with sclerosing cholangitis coming to reconstructive surgery or transplantation, approximately 10% will have an associated cholangiocarcinoma. In your series, only 1 of 40 patients had cholangiocarcinoma, which is a lower incidence than in the transplant series from Pittsburgh or the reconstructive series from Johns Hopkins. Did you have any other cholangiocarcinomas that were incidental findings in the hepatectomy specimens?

Liver transplantation in patients with sclerosing cholangitis is said to be difficult because of problems with ongoing sepsis, prior biliary tract surgery or, in patients with ulcerative colitis, prior colonic surgery. Have you analyzed the influence of prior biliary or colonic surgery on operative time, blood loss, or postoperative complications in your patients with sclerosing cholangitis? Moreover, you stated that there were no operative deaths among these patients. How do morbidity and mortality in patients with sclerosing cholangitis differ from your series as a whole? Is it really more difficult to transplant patients with sclerosing cholangitis who have had prior surgery?

Another important issue in liver transplantation is whether the disease for which the transplant is being performed will recur. Sclerosing cholangitis probably has multiple etiologies. However, in patients with associated ulcerative colitis, one predominant theory is that an autoimmune disorder affects both the bile ducts and the colon. As a result, immunosuppression therapy has been recommended both for patients with sclerosing cholangitis and for those with ulcerative colitis. Would you comment, therefore, on the possible role of your posttransplant triple-drug immunosuppressive therapy on the bile ducts and colon? Please also comment on the incidence of early rejection, late rejection, and the one patient with the vanishing bile duct syndrome who may have been a recurrence.

Finally, I am interested in the long-term follow-up of your patients. How does the 76% 5-year survival in your patients with sclerosing cholangitis compare with the survival of your other patients with benign disease? This question again relates to whether patients with sclerosing cholangitis undergoing prior biliary surgery are at higher risk. We have previously presented to this Association a similar number of patients with sclerosing cholangitis with dominant extrahepatic strictures managed with hepaticojejunostomy and long-term stenting. In 31 noncirrhotic patients who, by the Mayo model, might have had an expected 5-year survival of 20%, we now have a similar 75% 5-year survival. Thus, we still believe that a biliary bypass procedure is indicated in carefully selected noncirrhotic patients with mainly extrahepatic disease. Would you comment on the role of reconstructive surgery and how your results were influenced by these operations?

DR. GIL DIETHELM (Birmingham, Alabama): Dr. Britt, Dr. Jones, Members and Guests, Dr. Busuttil and colleagues have addressed the intriguing question regarding the interrelations between sclerosing cholangitis and ulcerative colitis. They have used the clinical findings in the postoperative management of these patients to assess whether or not the disease recurs.

Really the broad question here is whether or not the primary disease recurs in the recipient liver. If so, why? And what are the factors that lead to that? There has been considerable discussion, interest, and review of patients undergoing renal transplantation with recurrent disease, and it might be worthwhile to think about that. First of all, we know that lupus nephritis in an active phase can be transplanted to the recipient kidney. It occurs rarely, but has been reported. Wegener's granulomatosis, the same thing. Diabetes is a little different subject, but has been known as a recurrent disease. So regarding the question of whether or not recurrent disease exists, clearly, the answer is yes. Perhaps the best example of recurrent disease was described in the late 1950s by Drs. Merrill and Murray at the Brigham, and Professor Hamburger in Paris. Both of them noted and conclusively determined that nephritis can be transmitted to the recipient patient, and this occurred in the identical twin; therefore, rejection was not a problem. Thus, recurrent disease occurs, and we know about that history.

The question today is a little more complicated, and that is, whether chronic ulcerative colitis causes the disease in the liver, whether the liver itself has any relationship to the disease in the colon; perhaps neither are true. Perhaps there is another disease that affects both the liver and the colon, and Dr. Busuttil addressed this early on in his discussion about shared epitopes between the epithelia of the colon and the bile duct.

I think the question of whether or not an elevated alkaline phosphatase is evidence of recurrent disease is a little bit problematic. It will take several more years, perhaps 5 to 10, to determine whether or not that is truly the case. I think it is a little bit surprising and gratifying that recurrent disease has not been documented thus far, and that certainly might be what one would suspect because there is little evidence, at least as of now, that the primary disease is immunologic in origin, although it is an attractive hypothesis.

I have several questions, and I would like to raise them for Dr. Busuttil. First of all, we have discussed the immunologic background for the cause of the two diseases, and I would like your thoughts on that. And, secondly, I really wonder if the disease that we have described in the colon is always related to the liver. You have told us that it happens in only 70% of the cases, so 30% of the patients with chronic ulcerative colitis do not get liver disease. So it is not exactly that the two go together.

Again, I would like to thank Dr. Busuttil for the opportunity to discuss the paper. I would like to emphasize the importance of the concept of recurrent disease, and I would like to take the optimistic approach that, thus far, the data support the fact that there is no strong evidence for recurrent disease in the excellent series presented today. Thank you.

DR. RONALD W. BUSUTTIL (Closing discussion): I would like to thank both of the discussants for their comments and their questions. Dr. Pitt, it is true that our 81% incidence of ulcerative colitis in patients with primary sclerosing cholangitis is higher than is reported, but it is not that much higher. If you look at the Mayo Clinic series, it is about 70%, so I think we are probably in the ballpark.

Why 30%, Dr. Diethelm, do not develop it, I do not know. Perhaps they die of their primary sclerosing cholangitis, and we do not see the development of ulcerative colitis in those patients. But I think liver transplantation is going to save those patients from dying of liver disease, with longer follow-up to determine whether they will develop the chronic ulcerative colitis.

Dr. Pitt, our incidence of cholangiocarcinoma in patients that are referred for liver transplantation for sclerosing cholangitis is between 10% and 11%. We had two incidental tumors that we did go ahead and transplant. The other patients had overt cholangiocarcinoma plus sclerosing cholangitis and, therefore, were omitted from this analysis because we could not compare them.

With regard to prior surgery, one third of the patients that we transplant for sclerosing cholangitis have major biliary reconstructive surgery. Twenty-five per cent have prior cholecystectomy. Has this affected our operative mortality rate? Our overall operative mortality rate in 850 cases is four deaths, so it obviously has not. Why doesn't immunosuppression work? I do not know, but it does not work, and that also has been studied. The Mayo Clinic has done a trial looking at steroids, and it has not worked in ulcerative colitis or in primary sclerosing cholangitis. There have been some preliminary studies with cyclosporine, and they have not worked. I personally do not think that immunosuppression alters the natural history of this disease because I do not think you can give a more potent immunosuppression than we are giving them. We are giving them triple, and some of these patients will get quadruple, immunosuppressant therapy, and it does not seem to alter the natural history of the disease. We have not seen vanishing bile duct syndrome in our group of patients with sclerosing cholangitis. I believe that this patient that we showed very well may have recurrent primary sclerosing cholangitis. He specifically did not have vanishing bile ducts because, if you look at other sections, his bile ducts were perfectly intact except for the slow reaction.

You wanted to know if the survival in this group of patients is different from survival of all of our other patients. Our 5-year survival for our entire series of patients for benign disease is exactly what you see here, 76%. So it is really the same.

You talked about biliary bypass. We differ with you a bit regarding advocating biliary reconstruction for these patients. It depends on whether the patients initially get referred to the general surgical service or whether they get referred to our liver service. Our algorithm is as follows: If we have a patient that has diffuse disease, we recommend that that patient have transplantation right off the bat. If the patient has a dominant stricture, we believe that that patient should have balloon dilatation. If the balloon dilatation is not successful, and it is only extrahepatic disease, we would not have any problem with doing one operation on the patient. We do not believe that the use of long-term stents adds anything to these patients because they get cholangitis, they become septic, and it adds to the postoperative complications. We believe that in the 25% of patients with sclerosing cholangitis that have documented gallstones, we would not hesitate to remove the gallbladder and then just watch those patients until they develop absolute indication for liver transplantation.

Dr. Diethelm, does the disease recur? I think it probably will recur, and I think that as we follow these patients for a longer time we probably will see more recurrences. This is not new with liver transplantation. With primary biliary cirrhosis (PBC), it was thought that the disease recurred, and there probably is a very, very small subset of patients that have recurrence for PBC; however, when we look at those patients critically, as was done by Roy Calne and his group, it was not recurrent PBC, but chronic rejection they were seeing. And I think that is very difficult sometimes to distinguish.

Regarding the increased alkaline phosphatase, I agree with you. It is too early to tell whether this will be a specific marker, but I think it goes along with what we already know. That 20% of patients who have chronic ulcerative colitis and no overt evidence of liver disease have elevated alkaline phosphatase. And this has been associated with a pericholangitis. I would like to thank all of the discussants for their comments.

Benefits of Quadruple Immunosuppressive Therapy in Recipients of Living Related Donor Kidneys

A Review of 855 Operations

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Eight hundred fifty-five living related donor transplant recipients were analyzed according to 15 potential risk factors with regard to patient and graft survival according to immunosuppression. Group I, 1968 to 1983, (n = 440 patients) received azathioprine and prednisone; group II, 1984 to 1987, (n = 229 patients) received triple therapy—azathioprine, prednisone, and cyclosporine; and group III, 1988–1991, (n = 186 patients), quadruple therapy—azathioprine, prednisone, cyclosporine, and Minnesota antilymphocyte globulin. Three important risk factors included immunosuppression, tissue typing, and race. Groups II and III had improved allograft survival over group I (p = 0.03). Patients with two haplotype matches had similar survival in all three groups. Kidney survival in one-haplotype–matched recipients improved in group II and was equal to that of the two-haplotype–matched patients in group III. Cyclosporine improved allograft survival in both races when combined with azathioprine and prednisone. Quadruple therapy improved early survival in one-haplotype black patients, even though long-term results remained better in whites. Cyclosporine did not improve graft survival in two-haplotype recipients. The addition of cyclosporine and quadruple therapy did not increase morbidity and mortality rates.

THE ADDITION OF cyclosporine to the immunosuppressive regimen of patients undergoing cadaveric renal transplantation has been of substantial benefit to the prolongation of allograft and patient survival. The use of cyclosporine in patients receiving living related donor kidneys suggested by Flechner et al.[1] in 1984 in a series of patients, including both human leukocyte antigen and haploidentical recipients, suggested that cyclosporine was steroid sparing, diminished the frequency of rejection, and was equal to the use of donor-specific blood transfusions. Because of the concerns regarding the nephrotoxicity of cyclosporine, many centers were cautious about including this drug in the immunosuppressive management of the living related donor recipient, anticipating that long-term renal injury might occur. Payne et al.,[2] Sollinger et al.,[3] and Deierhoi et al.[4] suggested the addition of Minnesota antilymphocyte globulin to cyclosporine, azathioprine, and prednisone and used the term quadruple or sequential therapy for recipients of cadaveric kidneys. The data of Flechner et al.[1] were supported by subsequent studies of Hodge et al.,[5] using third-party transfusions with cyclosporine. Albrechtsen et al.,[6] in a prospective trial of cyclosporine and prednisone *versus* azathioprine-antilymphocyte globulin in renal allograft recipients of living related donor kidneys, noted similar results in both groups, but the steroid-sparing effect was obvious in the cyclosporine group.

Comparing the clinical outcome of patient and allograft survival with various regimens of immunosuppressive therapy in recipients of cadaveric patients is complicated by various factors, including source of donor kidney, method and duration of preservation, race, primary disease, tissue typing, current and peak panel-reactive antibody (PRA), and number of transplants. The use of living related one- and two-haplotype–matched recipients includes the benefit of a controlled genetic relationship between the donor and recipient, and therefore the interpretation of graft survival should allow a more accurate appraisal of the immunosuppressive therapy used in each study group.

This study is a retrospective analysis of 855 renal transplant procedures in 812 patients receiving one- and two-

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haplotype–matched recipients from living related donors from 1968 to 1991. The patients were divided into three groups comparing the effect of various regimens of immunosuppressive therapy on graft and patient survival and cause of death.

Materials and Methods

Clinical Material

This study includes 855 living related transplant operations in 812 patients from 1968 to 1991, analyzing 15 potential risk factors and their interactions. These risk factors include age, sex, race, donor age and sex, haplotype match, antigen match, peak and current PRA, donor relationship, immunosuppressive therapy, donor-specific blood transfusions, recipient renal disease, year of transplant, and number of retransplants (Table 1). Six hundred fifty-four patients were white and 201 black. Ages ranged from 10 to 67 years. There were 513 male and 342 female patients. All patients were transplanted at a single center and received post-transplant follow-up by the center transplant surgeons and nephrologists and by their referring nephrologist. Eight hundred nine patients received primary transplants, and 46 patients were transplanted more than once. The causes of renal failure are outlined in Table 2.

The patients were divided into three groups, depending on the immunosuppressive therapy administered: group I, 1968 to 1983 (440 transplants), received azathioprine and prednisone. Group II, 1984 to 1987 (229 transplants), received azathioprine, prednisone, and cyclosporine. Group III, 1988 to 1991 (186 transplants), received azathioprine, prednisone, cyclosporine, and Minnesota antilymphocyte globulin for one-haplotype patients. Two-haplotype–matched recipients received the same treatment as group II.

The initial azathioprine dosage was 4 to 5 mg/kg/day and tapered to 100 to 125 mg/day. The initial prednisone dose in groups I and II was 4 to 5 mg/kg/day, with a taper to 30 mg/day at 1 month and 15 mg/day at 6 months. In group II, cyclosporine was started at 10 mg/kg by the oral route, when the serum creatinine was less than 3 mg/dL, with blood levels ranging between 125 and 250 ng/mL by radioimmunoassay (Sandoz Pharmaceuticals, East Hanover, NJ). The usual cyclosporine dosage 30 days after operation ranged between 3 and 8 mg/kg, with a serum level of 125 to 250 ng/mL. Occasionally cyclosporine was administered by the intravenous route at one-third the oral dosage. In group III, the azathioprine dosage was similar to that of groups I and II. The starting prednisone dosage in this group was 30 mg/day and reduced to 15 mg/day at 30 days and to 10 mg/day between 30 and 90 days after operation. Minnesota antilymphocyte globulin was administered (intravenously) for 3 to 8 days, beginning on the day of operation. The initial dose was 10 mg/kg and 20 mg/kg/day thereafter intravenously for 5 to 7 days. The duration of Minnesota antilymphocyte globulin was determined by the serum creatinine, and the Minnesota antilymphocyte globulin was discontinued when the serum creatinine was less than 3 mg/dL, at which time cyclosporine was started.

TABLE 1. *Potential Risk Factors*

Immunosuppressive therapy
Recipient race
Haplotype match
Renal disease
Donor age
Recipient age
Donor sex
Recipient sex
Relationship of donor
Antigen match
Peak panel-reactive antibody
Current panel-reactive antibody
Donor-specific blood transfusions
Year of transplant
Number of retransplants

TABLE 2. *Renal Disease*

Disease	Frequency	%
GN	338	40.0
Diabetes	129	15.0
Unknown/other	95	11.0
Tubular interstitial	94	11.0
Vascular	81	9.0
Hereditary	80	9.0
Collagen–Vascular	31	4.0
Acquired	7	1.0

Histocompatibility matching with human leukocyte antigen typing was performed in all patients. Blank donor/recipient antigens were not counted as a match when calculating the number of matched HLA—A, B, or DR antigens. Panel-reactive antibody determinations were performed using the Amos Mod Wash complement-dependent cytotoxicity assay. The cell panel consisted of 42 cells selected to cover as many known human leukocyte antigen phenotypes as possible. Cytotoxicity cross-matches were performed using historical and day-before-transplant sera. The cross-match profile used from 1968 through February 1989 consisted of Amos Mod Wash, 3-Wash, and extended incubation assays using mixed lymphocytes. The profile used from March 1989 to 1991 included split T and B cell cross-matches performed by both complement-dependent cytotoxicity and flow cytometry. The peak PRA was significantly higher in groups II and III with a maximum PRA of 100% (all patients had a negative cross-match at time of transplant). The current PRA in groups II and III are much higher than in group I.

After all data were verified, characteristics of the groups were compared by using chi square test and t test. Actuarial analysis of survival was accomplished by the Kaplan-Meier method, with the Gehan-Wilcoxon technique providing the p value for stratified curve comparison. A survivorship and a hazard function (the instantaneous risk in patients not yet experiencing graft loss) as a time-related event was determined by the parametric model of Blackstone, Naftel, and Turner.[7] The model identified an early (0 to 6 months) and constant phase. The incremental risk factors for graft loss were determined for each phase. The constant phase begins at time 0. Its effect becomes relatively important after the early phase diminishes at about 6 months. Variables were considered important only if their p value was less than 0.05. All confidence limits were expressed as 70%. Graft loss was considered to be at the time of nephrectomy, return to dialysis, or death if the graft was functioning. There were no exclusions for technical or nonimmunologic failures. All patients were followed for 3 months after graft loss to determine mortality rate.

The diagnosis of rejection was established by the clinical signs of fever, graft enlargement, and renal tenderness combined with the laboratory evidence of an increase in serum creatinine and blood urea nitrogen. This information was combined with evidence of rejection by renal scintigraphy, including a decrease in the effective renal plasma flow. Renal biopsy was used for confirmation if the diagnosis was in question. Allograft rejection was treated by daily administration of 1 g methyl prednisone intravenously for 3 days with or without an increase in oral steroids to 5 mg/kg/day and rapid reduction to a level of 30 mg/day in 7 to 10 days from onset of treatment. Few patients in the first postoperative year received more than two treatments for rejection. If reversal was not achieved after the first treatment, OKT3 monoclonal antibody was usually used in place of a second steroid bolus as a means of rescue therapy in groups II and III. OKT3 treatment included a dosage of 5 mg/day intravenously for 10 to 14 days until reversal of rejection was achieved. During OKT3 treatment, cyclosporine was reduced to 5 mg/kg or less and azathioprine decreased to 25 mg/day. Prednisone was continued at 30 mg/day.

The three groups were compared for demographic characteristics with no differences found by race, sex, or donor sex. There were more diabetic recipients in groups II and III compared with group I ($p = 0.001$) and more two-haplotype–matched patients in group I ($p = 0.01$). Almost all patients receiving donor-specific blood transfusions were in group II. The recipient ages were older in groups II and III than in group I ($p < 0.06$). Seven hundred fifteen donor patients were contacted by questionnaire, of whom 409 (57%) responded. One hundred twenty-one patients returned for examination.

Results

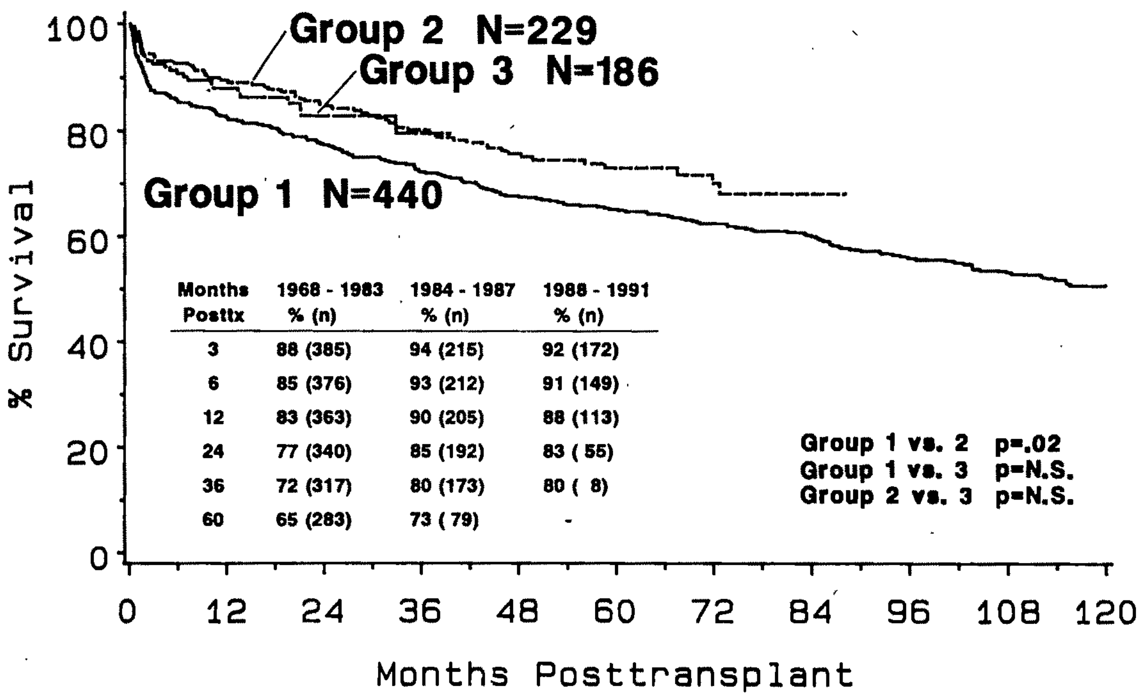
The mean graft survival of the 855 operations was 5 years 3 months, with a minimum of 3 months' follow-up for functioning grafts and a maximum follow-up of 22 years.

Patient and Graft Survival by Kaplan-Meier Analysis

Group I—1968 to 1983 (440 transplants)—received azathioprine and prednisone as immunosuppressive therapy (mean graft survival 7 years 5 months). The overall allograft survival at 1, 5, and 10 years was 83%, 65%, and 51%, respectively (Fig. 1). Two-haplotype–matched recipients had 1-, 5-, and 10-year graft survival of 91%, 80%, and 64%, and one-haplotype–matched recipients had graft survival of 79%, 58%, and 44%. There was no significant difference in allograft survival between the black and white races. The overall patient survival at 1, 5, and 10 years was 96%, 89%, and 80% (Fig. 2). Patient survival in two-haplotype–matched recipients at 1, 5, and 10 years after transplantation was 98%, 92%, and 81% (Fig. 3), and in one-haplotype recipients at the same time interval was 95%, 88%, and 80% (Fig. 4).

Group II—1984 to 1987 (229 transplants)—received azathioprine, prednisone, and cyclosporine as immunosuppressive therapy (mean graft survival, 4 years 2 months). The overall 1-, 2-, and 5-year graft survival was 90%, 85%, and 73%, respectively (Fig. 1). White recipients had better graft survival than blacks ($p = 0.0008$), with the difference in graft survival increasing after 3 months (Fig. 5). White/black graft survival at 1, 2, and 5 years was 92%/81% at 1 year, 88%/74% at 2 years, and 78%/59% at 5 years. The predominant difference in graft survival between the two races was in the one-haplotype patient ($p = 0.003$), the black one-haplotype recipient with a functioning graft had 79% 1-year survival (Fig. 6) compared with the white one-haplotype recipient (Fig. 7) of 92%. Two-haplotype–matched white and black recipients had similar results. The overall patient survival at 1 and 5 years was 97% and 93% (Fig. 2). The patient survival in one-haplotype recipients at the same time interval was 97% and 93% (Fig. 4), and in two haplotype recipients was 100% and 96% (Fig. 3).

Group III—1988 to 1991 (186 transplants)—with a mean graft survival of 1 year 5 months received azathioprine, prednisone, cyclosporine, and Minnesota antilymphocyte globulin (quadruple therapy). The overall graft survival at 1 year was 88%, and at 2 years was 83% (Fig. 1). There was no significant difference in graft survival between the two races (Fig. 8). When the one-haplotype recipient in each race was compared with groups I, II, and III, the blacks in group II showed little benefit with the addition of cyclosporine compared with the white recipient. In group III, the white recipient demonstrated no

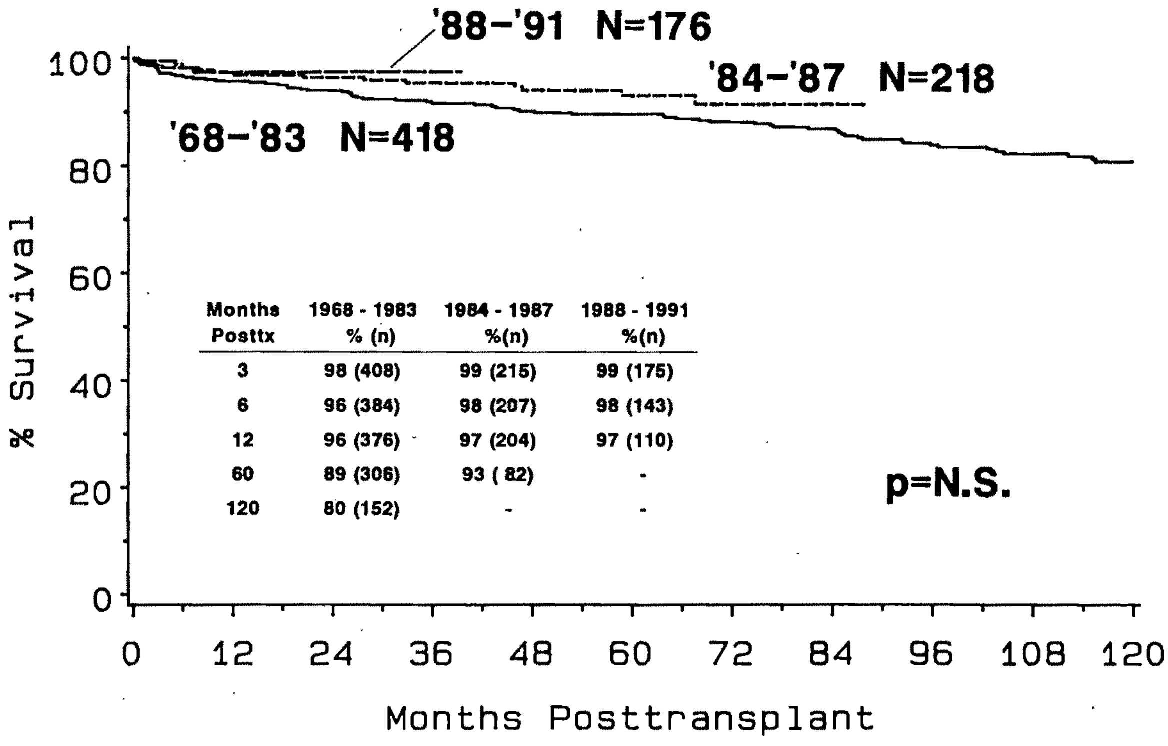


Months Posttx	1968 - 1983 % (n)	1984 - 1987 % (n)	1988 - 1991 % (n)
3	88 (385)	94 (215)	92 (172)
6	85 (376)	93 (212)	91 (149)
12	83 (363)	90 (205)	88 (113)
24	77 (340)	85 (192)	83 (55)
36	72 (317)	80 (173)	80 (8)
60	65 (283)	73 (79)	-

Group 1 vs. 2 p=.02
Group 1 vs. 3 p=N.S.
Group 2 vs. 3 p=N.S.

FIG. 1. Overall allograft survival at 1, 5, and 10 years.

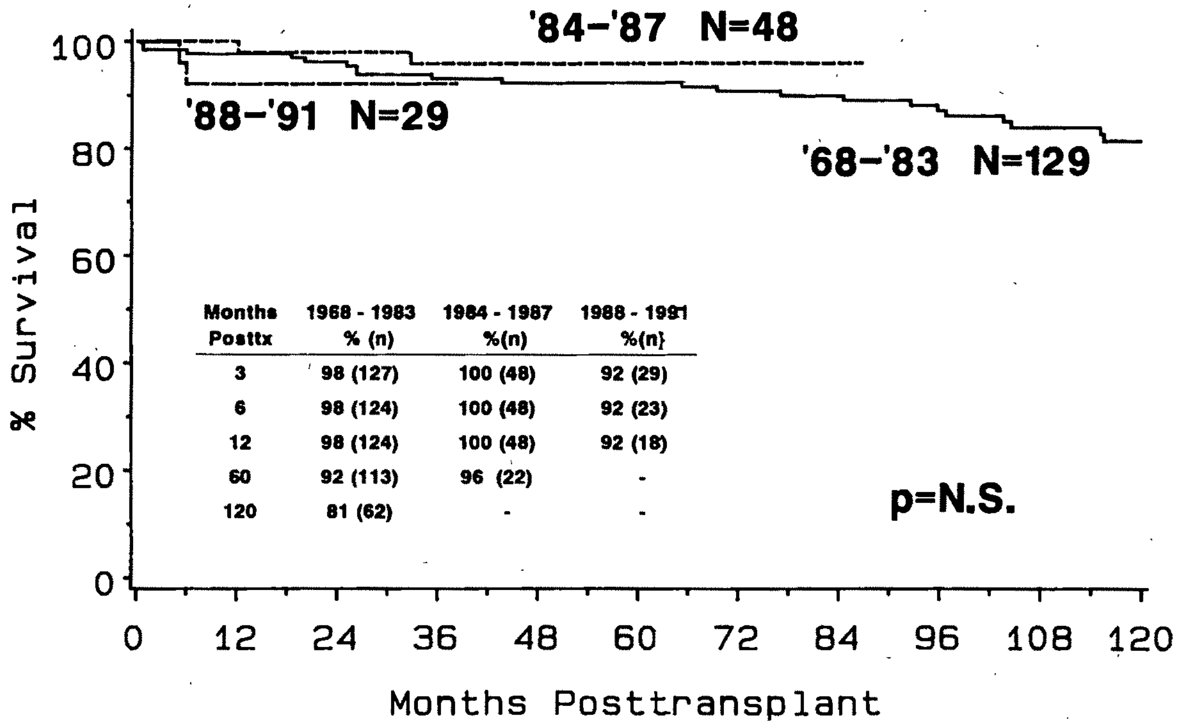
improvement with the addition of Minnesota antilymphocyte globulin. The black recipient showed improved graft survival with Minnesota antilymphocyte globulin but not equal to that of the white recipient (Figs. 6 and 7). The overall patient survival at 1 and 3 years was 97% and 97% (Fig. 2). The patient survival in one-haplotype recipients at the same time interval was 99% and 99% (Fig. 4), and in two-haplotype recipients was 92% and



Months Posttx	1968 - 1983 % (n)	1984 - 1987 %(n)	1988 - 1991 %(n)
3	98 (408)	99 (215)	99 (175)
6	96 (384)	98 (207)	98 (143)
12	96 (376)	97 (204)	97 (110)
60	89 (306)	93 (82)	-
120	80 (152)	-	-

p=N.S.

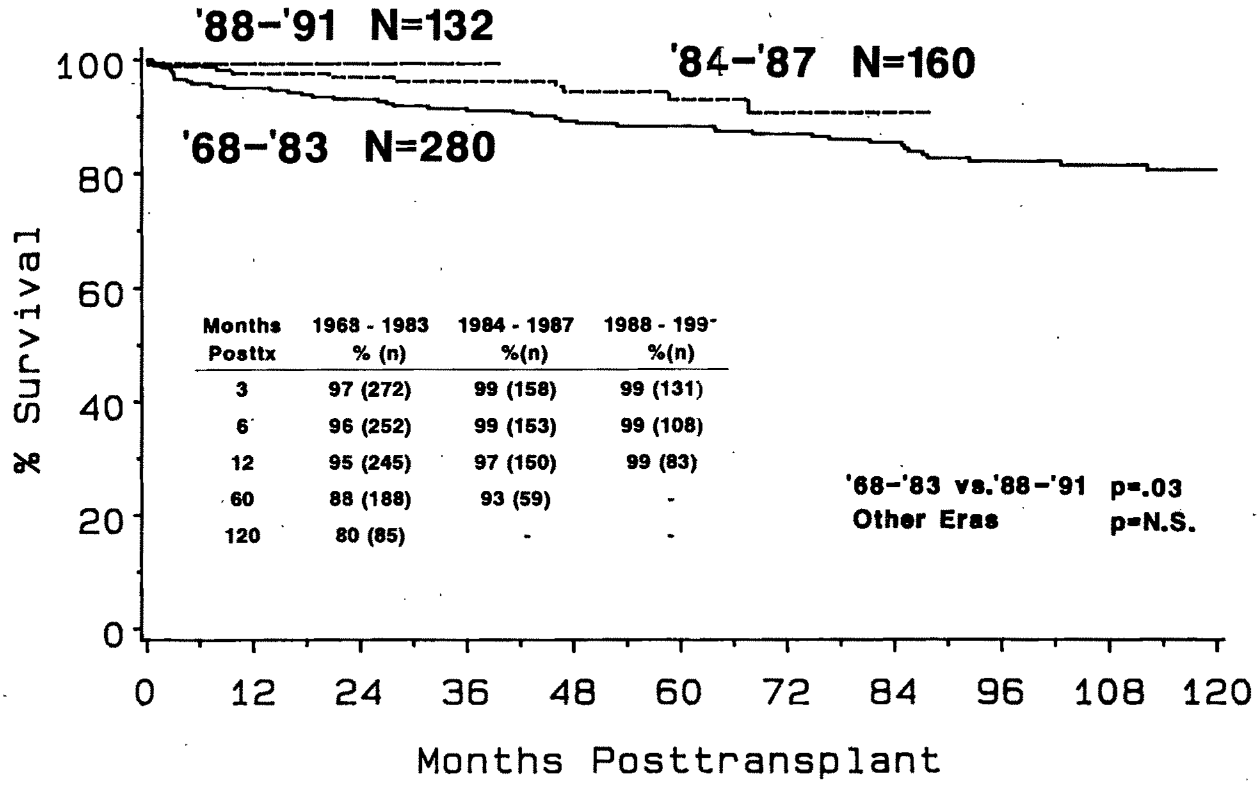
FIG. 2. Overall patient survival at 1, 5, and 10 years.



Months Posttx	1968 - 1983 % (n)	1984 - 1987 %(n)	1988 - 1991 %(n)
3	98 (127)	100 (48)	92 (29)
6	98 (124)	100 (48)	92 (23)
12	98 (124)	100 (48)	92 (18)
60	92 (113)	96 (22)	-
120	81 (62)	-	-

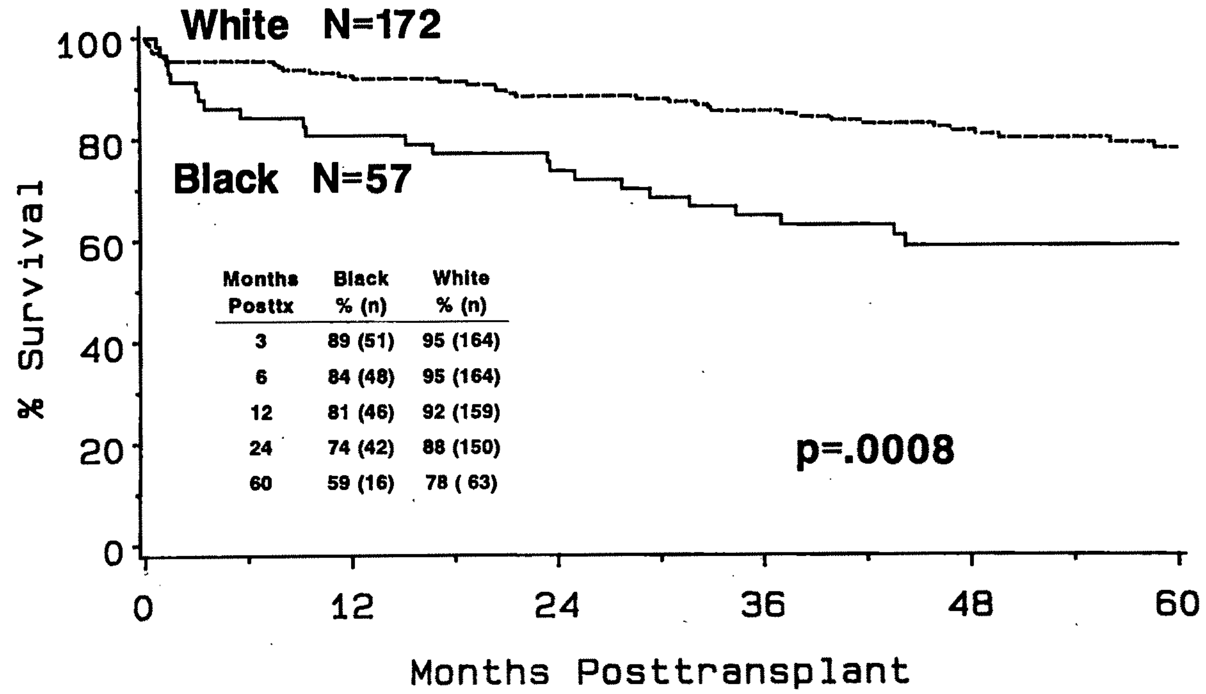
FIG. 3. Two-haplotype–matched patient survival compared by era in the three groups.

92% (Fig. 3). A comparison of allograft survival in recipients of living related donor and cadaveric kidneys (n = 551) during 1988–1991 confirms the benefits of living related donor grafts (p = 0.0001). The cadaveric/living related donor kidney survival at 1 and 2 years was 75%/88% and 68%/83%, respectively.



Months Posttx	1968 - 1983 % (n)	1984 - 1987 %(n)	1988 - 199 %(n)
3	97 (272)	99 (158)	99 (131)
6	96 (252)	99 (153)	99 (108)
12	95 (245)	97 (150)	99 (83)
60	88 (188)	93 (59)	-
120	80 (85)	-	-

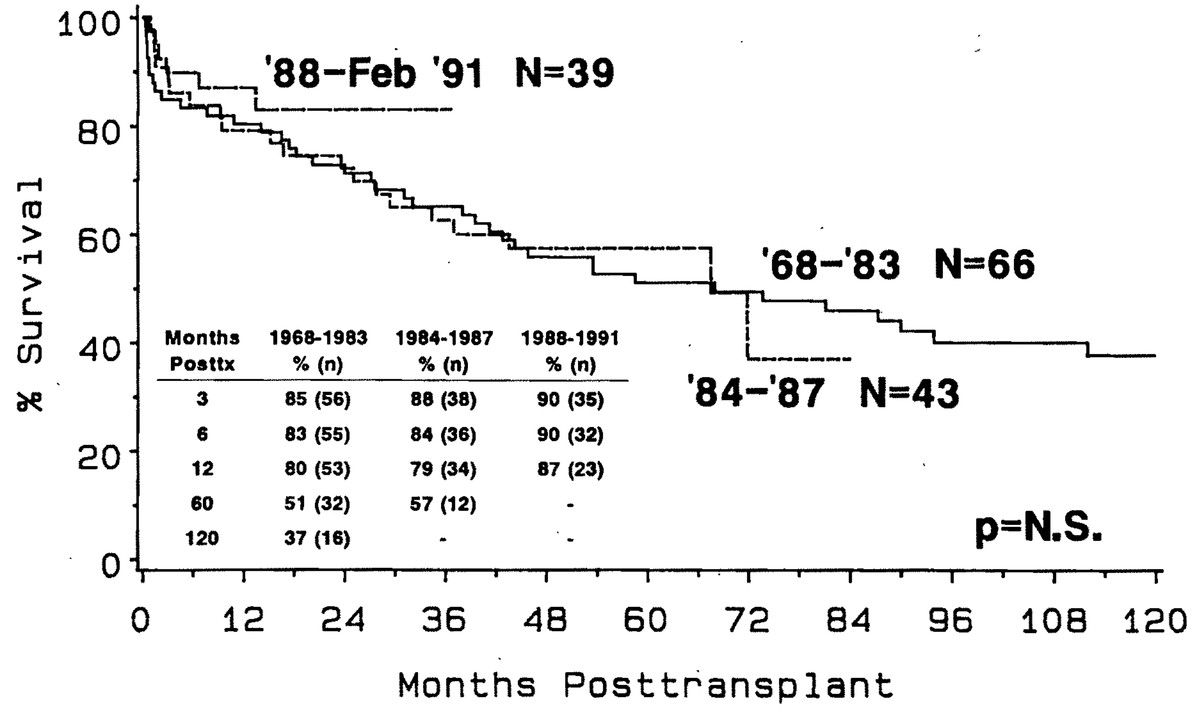
FIG. 4. One-haplotype–matched patient survival compared by era showed a significant improvement between groups I and III.



Months Posttx	Black % (n)	White % (n)
3	89 (51)	95 (164)
6	84 (48)	95 (164)
12	81 (46)	92 (159)
24	74 (42)	88 (150)
60	59 (16)	78 (63)

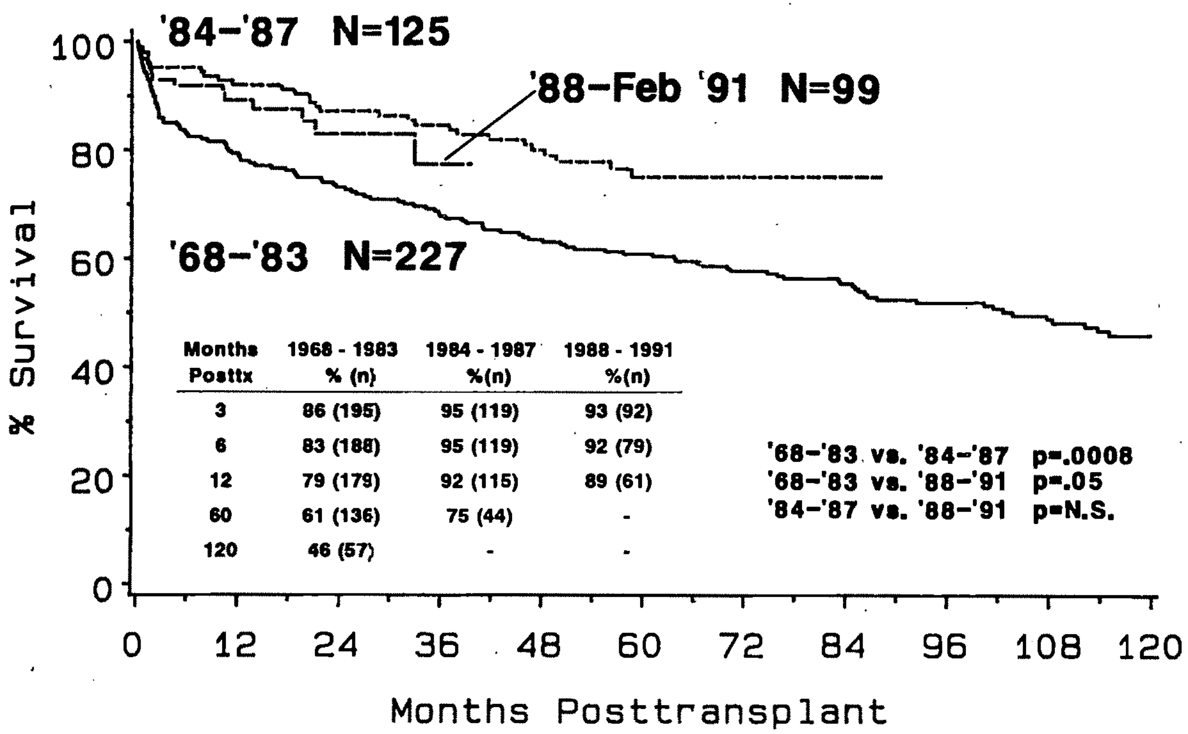
FIG. 5. Group II separated by race shows marked improvement in allograft survival in the white patients compared with black patients.

The parametric analysis was used to examine concomitant risk factors noted in the early phase, included the absence of cyclosporine (p = 0.002) and one-haplotype–matched recipients (p = 0.01). In the constant phase, the significant risk factors were the one-haplotype–matched recipient (p = 0.05), black race (p = 0.0008), diabetic (p = 0.01) and increasing donor age (p = 0.002). To study the effect of cyclosporine and race, the parametric model



Months Posttx	1968-1983 % (n)	1984-1987 % (n)	1988-1991 % (n)
3	85 (56)	88 (38)	90 (35)
6	83 (55)	84 (36)	90 (32)
12	80 (53)	79 (34)	87 (23)
60	51 (32)	57 (12)	-
120	37 (16)	-	-

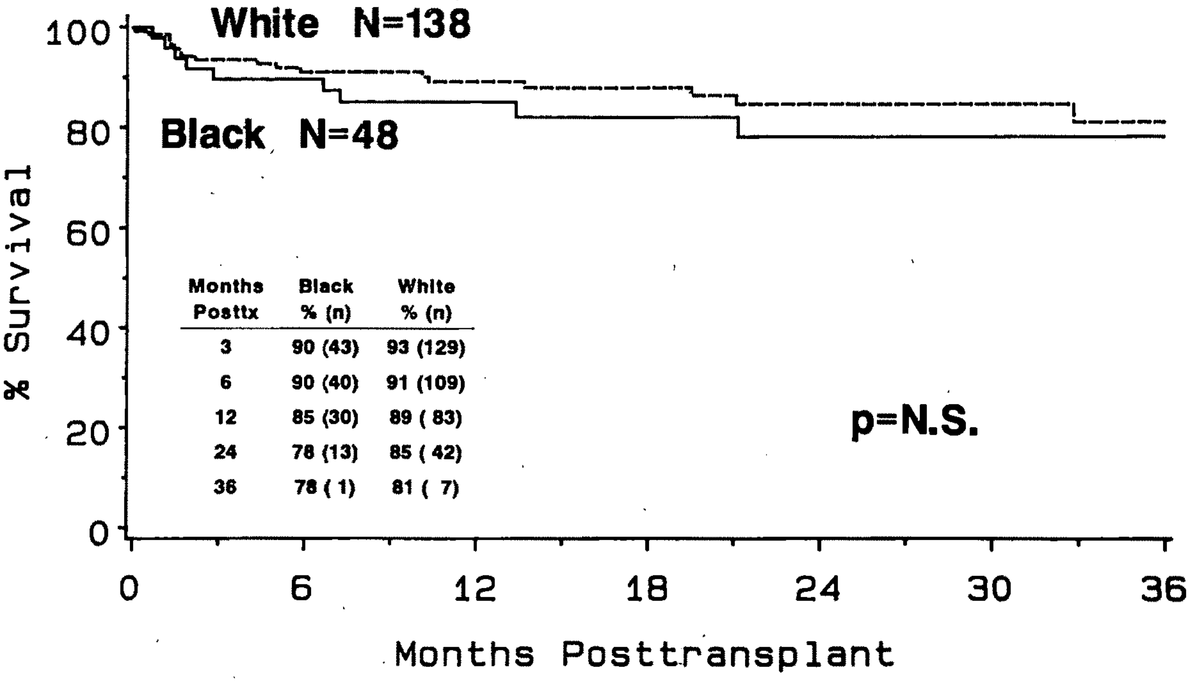
FIG. 6. One-haplotype–matched black patients in group III showed improvement in allograft survival compared with groups I and II, but the difference was not statistically significant.



Months Posttx	1968 - 1983 % (n)	1984 - 1987 %(n)	1988 - 1991 %(n)
3	86 (195)	95 (119)	93 (92)
6	83 (188)	95 (119)	92 (79)
12	79 (179)	92 (115)	89 (61)
60	61 (136)	75 (44)	-
120	46 (57)	-	-

FIG. 7. One-haplotype–matched white patients in groups II and III showed significant improvement in allograft survival over patients in group I.

was applied to a one-haplotype, nondiabetic patient receiving a kidney from a 37-year-old donor. The use of cyclosporine improved allograft survival in the early phase (first 6 months) in both races (p = 0.002). The constant phase became dominant at 6 months, at which time the blacks were at greater risk of graft loss (p = 0.0008). Figure 9 shows the hazard function. Table 3 shows the predicted allograft survival and the effect of cyclosporine and race.



Months Posttx	Black % (n)	White % (n)
3	90 (43)	93 (129)
6	90 (40)	91 (109)
12	85 (30)	89 (83)
24	78 (13)	85 (42)
36	78 (1)	81 (7)

FIG. 8. No difference was found in overall allograft survival between the two races in group III, suggesting that black recipients had improved graft survival with the addition of quadruple therapy.

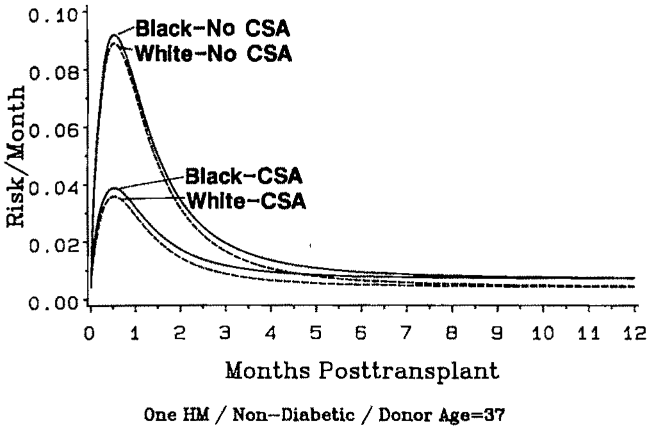


FIG. 9. The hazard function by parametric analysis for black and white patients shows the beneficial effect of cyclosporine.

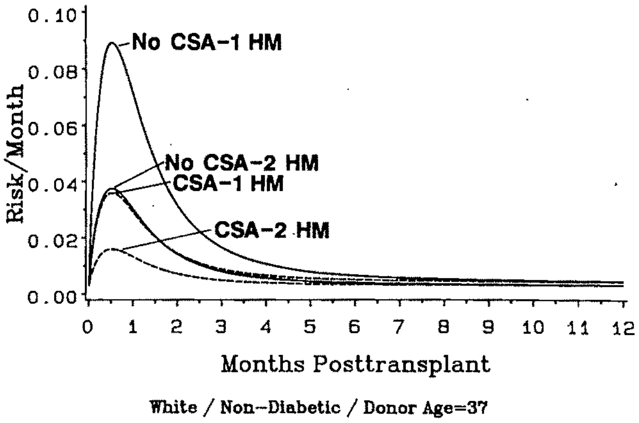


FIG. 10. Parametric analysis of one- and two-haplotype-matched recipients showed the effect of both typing and cyclosporine on instantaneous graft loss.

Parametric analysis compared tissue typing and cyclosporine and showed a beneficial effect by decreasing the risk for graft loss in both one- and two-haplotype–matched recipients. This effect was not found in the Kaplan-Meier analysis of the two-haplotype–matched patient. The two-haplotype–matched recipient was at less risk in both the early ($p = 0.01$) and constant phase ($p = 0.05$) (Fig. 10). The predicted allograft survival is shown in Table 4. Parametric analysis of all patients showed those with diabetes to be at greater risk in the constant phase ($p = 0.01$), as described in Figure 11 with a predicted allograft survival demonstrated in Table 5. Although donor-specific blood transfusion protocol improved allograft survival in the early phase, even when cyclosporine was administered, the improvement was not significant ($p = 0.06$).

Donor Follow-up

Four hundred nine of 715 donor patients (57%) contacted by questionnaire responded. There were no postoperative deaths within the first 6 postoperative months and no major complications in any of the 855 living related donors. In no instance did the operation contribute to the death of the donor. One patient was known to have developed end-stage renal disease 10 years after donor nephrectomy and required a transplant. One hundred twenty-one patients underwent a detailed postoperative examination, of whom 24% were black. The 121 donors were divided into groups according to the date of donor nephrectomy: group A 1968 to 1973 (n = 20), group B 1974 to 1978 (n = 25), group C 1979 to 1983 (n = 31), group D 1984 to 1988 (n = 45). There were no differences among the groups in respect to age, sex, race, mean arterial pressure (MAP), BUN, serum creatinine, proteinuria and estimated renal plasma flow at time of donation. On follow up there were no differences among the groups in respect to creatinine, blood urea nitrogen, glomerular filtration rate, proteinuria, or estimated renal plasma flow. Although the current MAP in Group A was greater than that of Group D ($p = 0.05$), the increase over time in the mean arterial pressure in Group A reflects a change consistent with an aging population. Black living related donors with a strong family history of hypertension had no greater increase in MAP than white living related donors during the follow-up period.

Cause of Recipient Death

There were 108 deaths in 812 patients undergoing 855 transplant operations (13%) with a maximum follow-up of 22 years. The average survival of those patients who

TABLE 3. *Predicted Survival: Effect of CsA and Race*

Months After Transplantation	Black		White	
	No CsA	CsA	No CsA	CsA
1	93%	97%	93%	97%
3	86%	93%	86%	94%
6	83%	91%	84%	92%
12	79%	87%	81%	90%
24	72%	80%	77%	85%
60	56%	62%	66%	73%

1 haplotype match, nondiabetic, donor age =37 yr.

TABLE 4. *Predicted Survival: Effect of Haplotype Match and CsA*

Months After Transplantation	1 Haplotype Match		2 Haplotype Matches	
	No CsA	CsA	No CsA	CsA
1	93%	97%	97%	99%
3	86%	94%	94%	97%
6	84%	92%	92%	96%
12	81%	90%	91%	94%
24	77%	85%	87%	91%
60	66%	73%	78%	81%

White, nondiabetic, donor age = 37 yr.

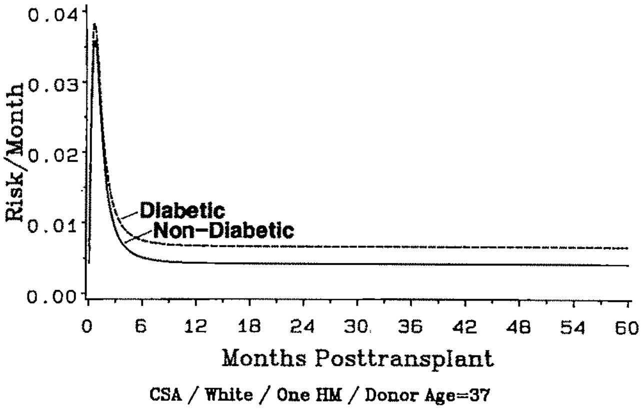


FIG. 11. The risks of allograft loss in diabetic *vs.* nondiabetic patients was examined with parametric analysis. There was no difference in the early phase, but decreased risk was seen for nondiabetic patients in the constant phase.

died was 5 years. The cause of death is noted in Table 6. Twenty-three deaths occurred overall in the first 6 months after transplantation (3%), 15 of which occurred in the first 3 months (2%). Eighty-five of the 108 deaths occurred after 6 months. The time of death was related to the origin. Fifteen patients who died of carcinoma, all with a functioning graft, had an average survival of 8 years 10 months. Cardiac deaths occurred in 26 patients, and all but two had a functioning graft, with an average survival of 6 years 7 months (only three died within 6 months). Ten of the 26 patients with cardiac deaths had diabetes. Two of seven patients with a cerebrovascular accident died within 6 months. Fifteen patients died of infection, with a mean survival of 2 years 3 months, six of whom died in the first 6 months. Sixteen patients died of septicemia, with four deaths in the first 6 months. In group I (n = 418), there were 89 deaths, of which 19 (5%) occurred in the first year. In group II (n = 218), there were 15 deaths, of which seven (3%) occurred in the first year. In group III (n = 176), there were four deaths (2%), of which all occurred in the first year. Sixty-six patients had less than 1 year follow-up.

TABLE 6. *Cause of Death (n = 108)*

Cause of Death	Frequency
Cardiac	26 (24%)
Septicimia	16 (15%)
Carcinoma	15 (14%)
Infection	15 (14%)
Unknown	14 (13%)
Cerebrovascular accident	7 (6%)
Trauma	4 (4%)
Gastrointestinal bleed	2 (2%)
Leukoencephalopathy	2 (2%)
Liver failure	2 (2%)
Pancreatitis	2 (2%)
Vascular	2 (2%)
Pulmonary emboli	1 (0%)

Cause of Graft Loss

Early graft loss due to rejection in the first postoperative year included 122 transplants, of whom 82 (67%) lost the kidney in the first 3 months. Sixty-seven of the 122 transplants (55%) failed in the first year because of acute rejection. Nineteen other kidneys failed because of chronic rejection and 20 patients died of other reasons with a functioning graft. The other 16 patients had graft loss to other reasons (Table 7).

TABLE 5. *Predicted Survival: Effect of Diabetes*

Months After Transplantation	Diabetic	Nondiabetic
1	97%	97%
3	93%	94%
6	91%	92%
12	87%	90%
24	80%	85%
60	63%	73%

CsA, white, 1 haplotype match, donor age = 37 yr.

Discussion

Cyclosporine has had a major impact on preventing allograft rejection and therefore prolonging graft survival in the recipient of cadaveric organs. This drug was found to be especially valuable when combined with azathioprine and prednisone as triple-drug therapy. The addition of Minnesota antilymphocyte globulin to triple-drug management as induction therapy for cadaveric recipients (quadruple therapy) avoided the nephrotoxic effects of cyclosporine and provided additional therapeutic coverage until satisfactory blood levels occurred.[3] The 1-year cadaveric kidney allograft survival now ranges from 75% to 90%, providing a 15% to 20% improvement before the introduction of cyclosporine. The data from the 812 patients with 855 transplants in this study examines the question of whether or not cyclosporine improved allograft survival in recipients of a living related graft, and if

TABLE 7. *Cause of Graft Loss in the First Postoperative Year (n = 122)*

Cause	Frequency
Acute rejection	67 (55%)
Death with functioning graft	20 (16%)
Chronic rejection	19 (16%)
Arterial thrombosis	4 (3%)
Recurrent renal disease	4 (3%)
Hyperacute rejection	3 (2%)
Acute tubular necrosis	1 (1%)
Arterial occlusion	1 (1%)
Infection	1 (1%)
Renal artery stenosis	1 (1%)
Ureteral necrosis	1 (1%)

so, was the effect similar in the one- and two-haplotype–matched patient. It is equally important to determine whether or not long-term cyclosporine nephrotoxicity occurred and had a negative impact on long-term graft survival. The data in this analysis showed no evidence that long-term cyclosporine was deleterious to renal function; however, frequent dosage adjustments were required according to blood levels. These findings were similar to those observed by others.[8-10]

The 440 transplant operations in group I were compared with the 229 transplants in group II, and the results support the positive influence of cyclosporine when combined with azathioprine and prednisone on prevention of graft rejection (Fig. 1). The improvement in overall graft survival in group I compared with group II was 83% to 90%, respectively (p = 0.02). The addition of Minnesota antilymphocyte globulin to triple-drug therapy (quadruple therapy) in group III did not improve the overall graft survival. When the patients in groups II and III were subdivided according to one- and two-haplotype matches, the two-haplotype–matched group showed little improvement, recognizing the patient numbers were small, whereas graft survival in the one-haplotype–matched recipient was increased. When group II was separated according to race, the graft survival was considerably better in the whites (p = 0.0008) (Fig. 5). This racial difference was not apparent in group III, in part because of the increase at 1 year in overall graft survival of the black patient and a slight decrease in survival in the white patient. The explanation for the marked improvement in the white one-haplotype match recipient in group II is unclear, but suggests that the immunologic disparity in the white patient is more easily controlled than in the black. The addition of Minnesota antilymphocyte globulin to the black one-haplotype match recipient also suggests that quadruple therapy may be helpful in graft prolongation; however, there was no statistical support for the statement.

In a previous publication,[11] we used the parametric model to explore risk factors participating in cadaveric graft survival. This model may have special relevance to the center concept and allows one to dissect the relevant and significant factors as they related to allograft survival. The parametric analysis allowed the examination of concomitant risk factors into an early phase with a higher risk for graft loss (0 to 6 months) and a constant phase (beyond 6 months) with a minimal rate of loss. The comparison of tissue typing and cyclosporine showed, as expected, a beneficial effect of cyclosporine on allograft survival in both the one- and two-haplotype–matched recipients (Fig. 10). The same benefit was noted when the risk for graft loss was much greater in the early phase in those patients in group I compared with groups II and III. Using the parametric analysis, the effect of cyclosporine and race can be predicted as noted on Table 3, and the same survival can be predicted for the haplotype-matched patient receiving cyclosporine (Table 4).

The failure of the addition of cyclosporine to markedly improve graft survival in the two-haplotype–matched recipient was surprising. This study did not discriminate between graft loss due to death of the patient and acute or chronic rejection. Therefore, in the event of death, there is a decrease in graft survival. It is important to emphasize that septicemia or other types of infection were not increased in groups II and III, which implies that the addition of the immunosuppressive effects of cyclosporine did not contribute to diminished host defense mechanisms. Similar findings have been noted by Hesse et al.[12] and Kostakis et al.[13]

There was no statistical difference in patient survival in the three groups (Fig. 2). The patients receiving two-haplotype–matched allografts had 1-year survival of 98%, 100%, and 92% in groups I, II, and III, respectively. The increase in patients with a greater postoperative risk such as diabetes and older age recipients in groups II and III had little effect on mortality rate. The cause of graft loss due to acute and chronic rejection in the first postoperative year was noted in Table 7. Sixteen per cent of the patients died with a functioning graft, and the other 13% of kidneys failed for a variety of reasons.

The relationship of graft survival may be inversely related to patient survival if the immunosuppressive effect is excessive, sacrificing patient survival for graft survival. In those circumstances, improved graft survival may occur by placing the patient at higher risk of death from infection. Thirty-one patients died of infection or septicemia; of these, 10 died in the first 6 months. When death was examined according to groups I, II, and III, the first-year mortality rate decreased from 5% to 3% to 2%, respectively. Thus, the improvement in allograft survival in groups II and III were not at the expense of patient survival, and the addition of cyclosporine and Minnesota antilymphocyte globulin were not a risk factor in increased patient mortality rate. Ota et al.[14] and Ferguson et al.,[15] using cyclosporine and prednisone in living related recipients, also found little difference in patient survival compared with a control series of azathioprine and prednisone, supporting our own observations.

The primary renal disease is always a consideration in the selection of patients for renal transplantation, and the long-term results are determined in part by the original disease leading to renal failure. Parametric analysis, shown in Figure 11, depicts the early hazard function to be the same in the diabetic and the nondiabetic. In the constant phase (after 6 months), however, the diabetic remains at a consistently higher risk for the next 4½ years. The predicted survival shown in Table 5 supports this observation, with deaths in this subgroup largely cardiac in origin. Graft loss in the constant phase of parametric analysis was usually the result of death of the patient with a functioning graft.

When allograft survival was compared in group III with a separate series of consecutive cadaveric recipients from our transplant center using quadruple therapy (n = 551), the patients in group III had much better survival (p = 0.0001). At 1 year, the cadaver and the living related survival was 75% and 88%, respectively. These results strongly support the continued use of the living related donor as long as the donor risk remains minimal, and are comparable to the data published by Perez et al.[16]

The clinical use of multiple immunosuppressive agents in various combinations has been shown in this study to be effective in graft prolongation, with a decline in patient mortality rate. It is of interest that black recipients continue to have a lower graft survival compared with the white patient, although this discrepancy was improved in group III. Surprisingly, in spite of the improvement in the graft survival in the one-haplotype–matched patient, the same immunosuppressive agents failed to significantly increase the survival in the two-haplotype–matched recipient, suggesting that those factors that contribute to the low incidence of rejection in this group are not easily controlled by current immunosuppressive therapy.

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DISCUSSION

DR. JOHN MCDONALD (Shreveport, Louisiana): Mr. Chairman, Ladies and Gentlemen, I am pleased to be asked to comment on this paper, which I genuinely do believe will be a standard of reference for many years. It is a study of some 855 renal transplants from living related donors accumulated over a period of 23 years. I think Dr. Diethelm and his group can certainly not be accused of premature publication. In fact, to the best of my knowledge, this is the largest such series ever published from a single institution. It demonstrates very clearly several points discussed by Dr. Diethelm, and the data are such that they really brook no argument.

I would like, therefore, to emphasize two points. The long-time benefit of renal transplants from living related donors is substantial, with 85% of haplotype match grafts in white recipients surviving in good health after 10 years. This is far better than can be achieved with any cadaver donor under any circumstance. Thus, the continued use of living related donors appears to me to be established and promises to continue to be indicated in the foreseeable future, in spite of suggestions to the contrary by others. Second, these data have been analyzed statistically to emphasize the fact that there are two risk phases: an early phase in which most grafts are lost, which lasts some 4 to 6 months, and a later phase in which graft loss is much less rapid but seems inexorable. Improvement of graft survival in the past 25 years has been largely in that early phase, where graft loss has been decreased from some 25% or 30% to 5% to 6%. This can be attributed to improved immunosuppression, and the whole process of improvement has been pharmacologically driven.

The persistent problem is the late phase, in which the shape of the curve has changed very little if at all in the last two to three decades and is now responsible for the bulk of graft loss. Thus, I would ask Dr. Diethelm his opinion as to how this late graft loss can be avoided. I personally doubt that it will yield to better immunosuppression regimens.

DR. F. O. BELZER (Madison, Wisconsin): I also appreciated reading the manuscript beforehand and being asked to make these few comments.

Again, I would like to re-emphasize all that Dr. McDonald said on this excellent study showing the benefits of living-related donation. In these 855 transplants, there was no donor death and only minimal donor morbidity. We always talk about cadaver kidneys and the results of cadaver transplantation. We never talk about those patients who never receive a kidney. And right now there will be many, many patients on the cadaver list who will never receive a kidney. This audience might be interested to know that if you look at the best diabetic transplant candidate age 10 to 24, after 5 years on dialysis, only 30% of these patients will be alive. If we take all diabetics on dialysis, only 19% will be alive after 5 years. So if you include the deaths on dialysis while awaiting a kidney, the result will be even more skewed favoring living-related transplantation.

Actually, Dr. Diethelm, we did exactly the same thing as you did, we stopped DST and we started quadruple immunosuppressant therapy several years ago with similar results as you presented. The only change we made is that we gave all patients ALG for 10 days, irrespective of renal function, hoping to stop most of the early rejection. I wonder if you are going to be doing this, because in your third group, the whites, there was no advantage to adding ALG.

My question to you is, were all patients in group 3 transfused? What is your policy on transfusions? Of course, in group 2, you have donor specific, but what did you do as far as transfusions in group 3? My second question is, what do you think is the role of DST in 1991? We personally still use it for two-haplotype mismatches and for living-unrelated donors, but we have not continued it for haploid-identical donor-recepient pairs.

My last question is, your third cause of death is carcinoma. We all know that malignany has increased in transplant recipients, but we have not seen that many cancers killing our patients. Of course, you had a very long follow-up, but I would be interested to find out what kind of cancers you had in your patient population.

Again, I appreciate discussing the papers.

DR. GIL DIETHELM (Closing discussion): I would like to thank Dr. McDonald and Dr. Belzer for their comments, and I would like to address Dr. McDonald's questions first.

First of all, the parametric analysis is a system that has been developed in our institution in the division of cardiovascular and thoracic surgery. And I think it allows one to look at graft survival and patient survival in quite a different way. It is a model that was developed by Drs. Gene Blackstone and Naftel and Turner in the department of surgery and statistics at the University of Alabama, and it has been popularized by Dr. John Kirklin, but it fits very well with transplantation and, I suspect, would fit very well with any other method of statistical analysis of patient survival. I would encourage you to look at it. The question of late graft loss pertains to the parametric model. It is true that late graft loss continues. It is also true that it is a problem of chronic rejection or humoral antibodies.

Dr. McDonald is exactly correct. The current drugs and the new drugs that are coming on the horizon will make a major impact on the prevention of acute rejection. The problem of chronic rejection continues. It is prevalent in cardiac transplantation, reflected as graft atherosclerosis. We see it in livers and liver transplantation. We see it in the kidney and, of course, the lung and the pancreas. So the late loss continues to be a problem and, I suspect, will be one of the major obstacles.

The discussion about the black *versus* the white patient in graft and patient survival is an ongoing one. And when I had group 1, that first group, to deal with, I was very proud that our patients did the same, the whites and the blacks. And I gave some papers and supported that. And then when we looked at the data of cyclosporine added onto azathioprine and prednisone in group 2, I could not believe that we had a .0008 difference. Now there is one potential flaw in this analysis. The statistics are correct because they are based on graft loss, whether it is by rejection or by death of the patient. I think we need to go back and re-examine how many patients died of a car accident, were hit by lightning, and so forth, that had normal graft function, because we are discussing immunologic survival. We are not discussing how long patients live otherwise. And that has been the basic ground-floor approach to statistical analysis in transplantation for many years. I do not quibble with it. But if we are going to look at two different areas, we perhaps ought to at least handle that in a statistically different manner. I am not totally sure that admixture is the entire issue, Dr. McDonald, and I suspect that there are a great number of admixture genetic relationships in all populations. But if you look at the European literature, the closer the genetic group, the better the results. And the United States is for sure an admixture in the real sense, and our results are less good. I am not sure that relates precisely to your question, but I have no doubt that admixture does play a role in the genetic disparity in recipients.

I will discuss the comments by Dr. Belzer just briefly: First of all, there is no question that living related donor transplant is best. Secondly, it is an elective operation. Thirdly, if done properly the patient will never see dialysis. The patient will never stop work except for the operation. And then, furthermore, if he had an HLA identical, his 5-year graft survival might be 94% or 95%. There is no alternative in terms of best treatment that surpasses the living related donor transplant.

Should we have used ALG for 10 days instead of 5? I think that is possible, and it might have made an impact in our results. I have the notion that 5 to 7 days of ALG rarely causes a major problem with viral infection, cytomegalovirus, and so forth. Ten to fourteen days seems to be the breakpoint. I will not quibble with whether 10 days is on the bad side or the good side. But as you go on with ALG there is definitely a risk factor.

As for the transfusion protocol, we used donor-specific transfusions for a number of years. There are two or three problems with this form of treatment. Number one, the patients often get sensitized at between 10% and 25%. Number two, when we followed our patients 3, 4, and 5 years, there was a decay factor. And although the first-year graft survival was significantly better with a good p value, 2 and 3 years later the patients' survival had decayed. And that goes back to the very first question of Dr. McDonald's. And that is, as you see the patients go out over the years, the graft loss is due to chronic rejection. So the benefits of donor-specific transfusions were lost at the second year. And what is the role of donor-specific transfusions in 1991? Well, I think pure donor-specific transfusion as we carried it out years ago I would not favor. Conversely, there may be newer techniques—you will hear about one shortly—that might make a large difference.

I think Dr. Belzer's point regarding the role of carcinoma was accurate. It was a high risk factor for us, but we had a long-term graft survival. They were out 5, 8, and 10 years. The most common was skin cancer and, interestingly, you almost never see skin cancer in the blacks; it is always in the whites and, on occasion, it is fatal. Thank you very much.

Efficacy of a Single Pretransplant Donor-specific Transfusion and Cyclosporin A Administered 24 to 48 Hours Before one-haplotype–Mismatched Living Related Donor Kidney Transplant

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During the 7-year period from March 1984 to June 1991, 86 haploidentical living related kidney recipients were entered into one of three donor-specific transfusion (DST) and cyclosporine treatment protocols: (1) Multiple pretransplant DSTs with cyclosporine begun after transplant, n = 34; (2) Multiple pretransplant DSTs with cyclosporine begun pretransplant, n = 31; and (3) a single DST 24 to 48 hours before transplant with intravenous cyclosporine initiated after the transfusion, n = 21. Triple immunosuppression (prednisone, azathioprine, and cyclosporine) was continued in all groups after transplant. The 1-year patient (97%, 97%, and 93%, p = not significant) and graft (91%, 90%, and 87%, p = not significant) survival were similar for the three groups. No differences were seen in the incidence of rejection at 1 year (61%, 45%, and 60%, p = not significant) or in the incidence of infectious complications (26%, 42%, and 47%, p = not significant). It is concluded that a single DST given 24 to 48 hours before operation followed by pretransplant cyclosporine is as effective as classic DST conditioning of recipients using either pretransplant or post-transplant cyclosporine. The single DST protocol has the advantage of not eliminating any donors because of sensitization and was less costly and easier to administer.

IN 1973 OPELZ ET AL.[1] REPORTED that random donor blood transfusion before cadaveric renal transplant improved allograft survival. The beneficial effects of blood transfusion were further documented by Salvatierra et al.,[2] who achieved a 38% improvement in 1-year graft survival after giving deliberate donor-specific blood transfusions (DST) before kidney transplants from one-haplotype–mismatched living related donors (LRD). All of the recipients had high responses of their lymphocytes against donor cells in mixed lymphocyte cultures (MLC). The protocol of three pretransplant DSTs, however, was complicated by sensitization to the proposed donor in 29% of the pairs.[2] Although this sensitization and elimination of recipients at a higher risk for rejections may in part account for the exemplary results of this study, the loss of 29% of potential donors was a significant disadvantage. Several studies have since demonstrated that the incidence of sensitization can be reduced to 8% to 14% through concurrent administration of azathioprine at the time of the initial transfusion and thereafter.[3–5]

The introduction of cyclosporine resulted in a remarkable increase in survival for both living related and cadaveric renal allograft recipients.[6] With cyclosporine, the graft survival advantage provided by transfusion decreased to approximately 5% in cadaveric transplants and to 2% to 3% in LRD one-haplotype–mismatched transplants when examined at 3 months and 1 year.[7] Similarly, the benefit of DST has been reduced to 3% to 9% in living related kidney recipients.[8,9] In light of the reduced benefits, the burden imposed on the donor and recipient by repeated pretransplant blood transfusions with pretransplant immunosuppression, and donor exclusion because of the persistent 10% incidence of sensitization, many centers have abandoned DST in LRD transplants. Recent studies, however, have suggested that DST can induce a specific suppression of the immune system, allowing a decrease in the requirement for nonspecific immunosuppression over the long term, with a coincident decrease in adverse effects, while maintaining or improving allograft survival.[9, 0]

Animal studies have demonstrated synergy between cyclosporine and DST given 24 hours before transplantation with no evidence of sensitization.[11–13] Furthermore, a clinical study treating human cadaveric transplant re-

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cipients with a single DST and cyclosporine infusion 24 hours before transplantation resulted in immunologic hyporesponsiveness to the donor (by MLC) and a decrease in severe rejection episodes requiring OKT3 treatment in the first 6 months after transplant.[14]

Since April 1989, we have adopted a protocol of giving a single pretransplant DST 24 to 48 hours before transplantation followed immediately by initiation of a cyclosporine infusion for one-haplotype–mismatched LRD renal transplant recipients to eliminate the sensitization caused by multiple DSTs. The safety and efficacy of this protocol is compared with two prior one-haplotype–mismatched LRD treatment protocols that used multiple pretransplant DSTs and cyclosporine initiated either before or after the transplant.

Materials and Methods

Patients

Eighty-six one-haplotype–mismatched LRD–recipient pairs were prospectively entered into a DST/cyclosporine treatment protocol and underwent transplantation between March 1984 and June 1991. There were no exclusionary criteria. Treatment protocols were approved by the Institutional Review Boards of the University of Cincinnati and The Christ Hospital.

Experimental Groups

Three sequential treatment protocols have been used during this period:

Group 1: Multiple pretransplant DSTs with cyclosporine initiated in the post-transplant period, n = 34. Recipients received approximately 150 mL fresh or stored donor whole blood or packed cells on three separate occasions at 2-week intervals. Three patients received two transfusions, and two patients received six transfusions (each had three stored and three fresh). Two weeks after the last transfusion, recipients underwent a final cross-match and were transplanted shortly thereafter. Recipients who developed a warm B-cell–positive cross-match after the last transfusion (4/34, 12%) were challenged with one or more additional transfusions and transplanted when the cross-match reverted to negative after this challenge. Seventy-one per cent of group 1 patients received continuous azathioprine immunosuppression (1 mg/kg/day initial dose, with adjustments in dosage according to the recipient's white blood cell count) during the period of DST administration. Two patients received buffy coat transfusions with RhoGAM (Ortho Diagnostic, Raritan, NJ) rather than whole blood or packed cells because of Rh incompatibility. Oral cyclosporine was initiated at a dose of 4 mg/kg twice daily after good renal function was established (mean, 5.31 ± 1.5 days after operation), except for one patient who developed severe acute rejection before initiation of cyclosporine.

Group 2: Multiple pretransplant DSTs with pretransplant cyclosporine, n = 31. This group was transfused using a protocol similar to that for group 1. All patients received three transfusions, except for one patient who developed a warm B-cell cross-match (given an additional fresh DST) and a patient whose transplant was delayed because of an upper respiratory tract infection (given a fourth fresh DST). Two patients were given buffy coat transfusions and RhoGAM to prevent Rh sensitization. Eighty-four per cent of the recipients received azathioprine immunosuppression concurrently with DST. Cyclosporine was started the day before transplantation as either an oral dose (4 mg/kg twice daily) (48%) or as a constant intravenous infusion (3 mg/kg/day) (52%). Patients were converted to oral cyclosporine in the post-transplant period as soon as they were able to take oral medications.

Group 3: Single pretransplant DST with pretransplant cyclosporine, n = 21. Recipients were transfused with 250 mL donor whole blood or packed cells 24 to 48 hours before their transplant (mean, 37.7 ± 2.44 hours). Three patients received buffy coat transfusions and RhoGAM. No patient in this group received azathioprine in the pretransplant period. An intravenous infusion of cyclosporine (3 mg/kg/day) was initiated immediately after the completion of DST and continued into the post-transplant period. Cyclosporine levels were measured approximately every 6 hours. At the time of transplantation, cyclosporine levels ranged from 289 to 932 ng/mL (mean, 494 ± 43 ng/mL) by whole blood polyclonal fluorescent polarization immunoassay (FPIA).[15] Conversion to oral cyclosporine was performed as early as possible. As a preliminary study, a subgroup of six patients were also given a single 2.5-mg (4 patients) or 5-mg (2 patients) dose of OKT3 immediately before the DST to assess the efficacy of pretransplant T cell depletion. All patients underwent hemodialysis before the OKT3 administration, but because of the concern regarding ablation of the DST effect, the patients were not pretreated with steroids before the OKT3.

Intraoperative and Post-transplant Immunosuppression

Immunosuppression was maintained after transplant using triple therapy (cyclosporine, azathioprine, and prednisone) in all groups. Cyclosporine was initiated according to treatment protocol. Cyclosporine doses were adjusted to maintain 12-hour whole blood trough levels during the first month at approximately 200 ng/mL, using a high-pressure liquid chromatography assay or 350 to

500 ng/mL by FPIA polyclonal assay. Azathioprine was given in a dose of 3 to 4 mg/kg intravenously in the operating room and then 1.5 mg/kg/day intravenously or orally, adjusted only for leukopenia. Methylprednisolone (Solu Medrol; UpJohn, Kalamazoo, MI) was given in a dose of 250 mg (groups 1 and 2) or 125 mg (group 3) intravenously in the operating room and prednisone (125 mg/day) (groups 1 and 2) or 1.0 mg/kg/day (group 3) was begun orally after transplant, and rapidly tapered to 20 mg/day with a more gradual taper over the first year as rejection episodes allowed. Rejection episodes were identified by a sudden and persistent elevation in serum creatinine and blood urea nitrogen associated with clinical findings of rejection in the absence of other causes of renal dysfunction. Percutaneous biopsy was performed if the diagnosis was in doubt or if rejection episodes failed to respond to initial therapy. Mild rejection episodes were treated initially with bolus injections of methylprednisolone (250 mg intravenously daily for up to 4 days). If there was no response or a worsening of renal function or if the initial biopsy showed moderate or severe acute cellular rejection or any component of acute vascular rejection, therapy was changed to OKT3 (5 mg/day intravenously for 7 to 14 days) or Minnesota antilymphoblast globulin (15–20 mg/kg/day intravenously for 7 to 14 days). In selected instances, refractory rejection in patients with contraindications to further high-dose immunosuppression were treated with local graft irradiation (150 rad/day for 3 days).

Outcome Variables

Treatment complications were compared, including presumptive evidence of cyclosporine nephrotoxicity within the first 14 days, indicated by a rise in creatinine managed by withdrawal or reduction in cyclosporine dose. Graft loss was dated as the time of return to chronic hemodialysis due to loss of graft function or time of transplant nephrectomy. Patient death from any cause was included as a graft loss. Actual and actuarial patient and graft survival were calculated at 1 year. Rejection episodes were compared at 6 months and 1 year. Severe rejection was defined as rejection requiring treatment with OKT3, Minnesota antilymphoblast globulin, or graft irradiation. Infectious complications within the first year were included if they required inpatient or outpatient antimicrobial therapy. Cytomegalovirus (CMV) infections were defined as clinical symptoms characteristic of CMV infection that correlated with an increase in CMV titers or positive CMV cultures.

Statistics

Statistical analysis was performed on the PC SAS system (version 5.04, SAS Institute, Inc., Cary, NC). Comparisons between groups were performed using the chi square test, Fisher's exact test, Wilcoxon rank sum test, t test, or one-way analysis of variance with Duncan's multiple range test, where appropriate. Graft survival curves were calculated using the product-limit survival estimates method (Kaplan-Meier). All means are reported as mean ± standard error of the mean. Significance was accepted if $p < 0.05$.

Results

There were no significant differences between treatment groups on the basis of sex, race, incidence of diabetes, primary disease process, or pretransplant panel-reactive antibody (Table 1). The patient-*versus*-donor MLC was

TABLE 1. *Recipient Characteristics*

	Group 1	Group 2	Group 3	
DST Protocol Cyclosporine	Multiple DST After Transplant	Multiple DST Before Transplant	Single DST Before Transplant	p
N	34	31	21	
Age (mean)	39.3 ± 2.0 yr	39.6 ± 2.1 yr	37.6 ± 2.6 yr	NS
Female	17/34 (50%)	10/31 (32%)	12/21 (57%)	NS
Race				NS
Black	5/34 (15%)	4/31 (13%)	4/21 (19%)	
White	28/34 (82%)	27/31 (87%)	16/21 (76%)	
Asian	1/34 (3%)	(0%)	1/21 (5%)	
Diabetes	12/34 (35%)	13/31 (42%)	6/21 (29%)	NS
Second transplant	1	3	0	NS
PRA (mean)	2.2 ± 2.0%	5.6 ± 1.2%	3.9 ± 2.8%	NS
MLC stimulation index (mean)	9.4 ± 2.8	11.8 ± 2.1	20.3 ± 4.5	<0.05 for 1 *vs.* 3
Third-party transfusions	19/34 (56%)	17/31 (55%)	11/21 (52%)	NS
Mean (units)	5.2 ± 1.7	7.7 ± 2.2	12.5 ± 5	
Median (units)	3	5	4	

DST, donor-specific transfusion; NS, not significant; PRA, panel-reactive antibody; MLC, mixed lymphocyte culture.

TABLE 2. *Donor Demographics*

Characteristic	Group 1	Group 2	Group 3	p
Age (mean)	37.2 ± 2.3 yr	35.4 ± 1.9 yr	33.3 ± 2.8 yr	NS
Female	8/34 (53%)	17/31 (55%)	7/21 (33%)	NS
Relation				NS
Parent	7/34 (20%)	4/31 (13%)	5/21 (24%)	
Sibling	17/34 (50%)	19/31 (61%)	9/21 (43%)	
Offspring	8/34 (24%)	8/31 (26%)	7/21 (33%)	
Other	2/34 (6%)	0%	0%	

NS, not significant.

significantly higher in the single-DST group (group 3 *versus* group 1), however. Approximately 55% of the patients from each group received third-party transfusions (Table 1), with a median of 3 to 5 units. Mean follow-up for the three groups varied from 72 ± 1.6 months for group 1 to 14.3 ± 1.6 for group 3. Analysis therefore was confined to the first year for statistical comparisons.

Donor characteristics (Table 2) were similar between groups.

Transplant Outcome

Initial graft function was excellent in all groups. Examination of the serum creatinine during the first 5 days disclosed no significant difference in initial function between groups; all groups had good early function (Fig. 1). The grafts continued to function well through the first year of follow-up, with a mean serum creatinine for all groups remaining below 1.7 mg/dL (Fig. 1). Patient survival at 1 year was uniformly good for all groups (Table 3). Two of the three patients who died within 1 year of transplant died as a result of nonimmunologic events. The single death in group 1 was a patient who committed suicide 18 days after transplant, and the death of a patient in group 3 was due to anaphylactic response to protamine sulfate during cardiac surgery at another institution 88 days after transplant. Both patients died with excellent graft function. One-year graft survival also was similar for all groups. Elimination of graft losses due to nonimmunologic-related deaths allowed for analysis of immunologic graft survival related to treatment protocol (Table 3) and also demonstrated no differences between groups. Actuarial graft survival curves are presented in Figure 2.

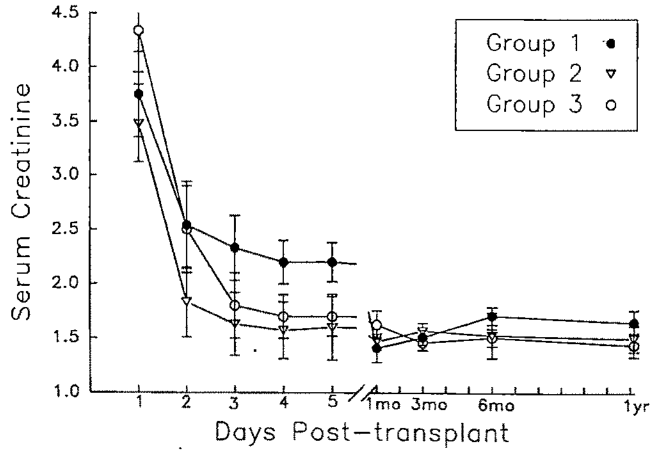


FIG. 1. Graft function.

TABLE 3. *Patient and Graft Survival*

Survival	Group 1	Group 2	Group 3*	p
1-yr patient survival	33/34 (97%)	30/31 (97%)	14/15 (93%)	NS
1-yr graft survival (all causes)	31/34 (91%)	28/31 (90%)	13/15 (87%)	NS
Corrected 1-yr graft survival (excluding death from suicide and allergic reaction)	31/33 (94%)	28/31 (90%)	13/14 (93%)	NS

* Includes only patients with follow-up longer than 1 year.
NS, not significant.

The prednisone doses for each group over the first year were not significantly different except at 6 months, when the doses for both groups receiving pretransplant cyclosporine were significantly lower. This effect was lost by 1 year (Fig. 3). All patients continued to receive steroids by the end of the first year, but many were subsequently withdrawn from this drug (comparison of groups not possible at this time).

Rejection

There were no hyperacute rejections seen in any of the groups, but all had a similar incidence of early rejections described in DST protocols.[16] Thirty-eight per cent of the recipients in the single-DST group (group 3) had a rejection episode within the first 14 days, compared with 23% in group 2 and 35% in group 1 (p = not significant). All but two of these rejection episodes resolved with antirejection therapy. One patient in group 3 and one in group 1 underwent transplant nephrectomy because of irreversible rejection at postoperative days 7 and 22, respectively. A third patient in group 2 recovered from an initial rejection episode at 13 days, but had two additional rejection episodes in the following 30 days and subsequently lost her graft on post-transplant day 56.

Fifty-two per cent of the patients receiving a single DST (group 3) had a rejection within the first 6 months, compared with 45% for group 2 and 56% for group 1 (Table 4). The rejection episodes in the single-DST group tended to be more severe, because 48% of the patients experienced a severe rejection during this period. This was not statistically different from the other groups, however. The patterns of rejection also were quite similar at 1 year. None

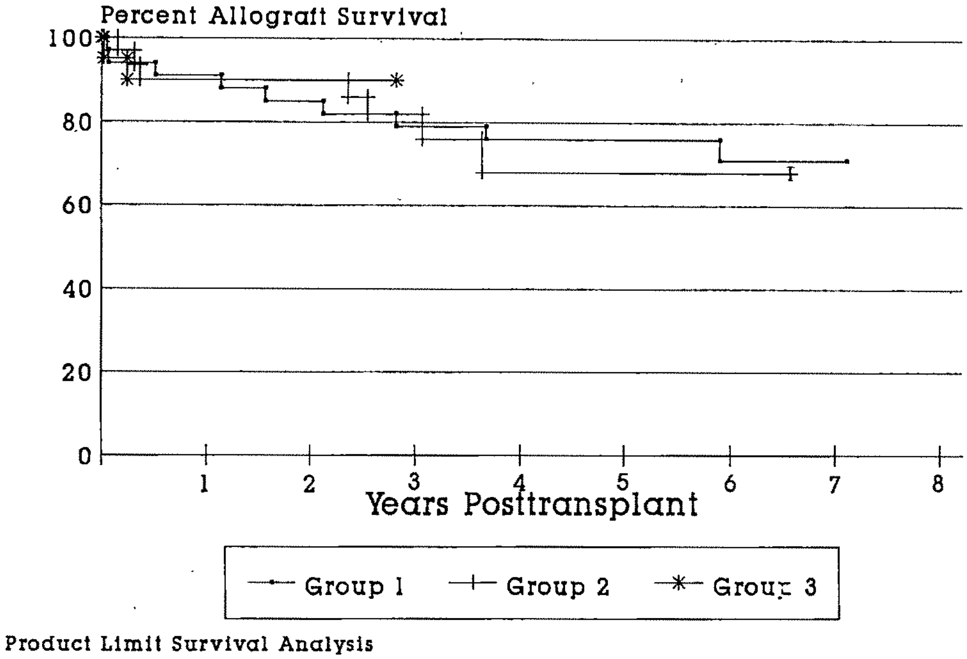


FIG. 2. Actuarial graft survival (no exclusions).

of the groups had a high incidence of patients experiencing more than one episode of severe rejection within the first year. Rejections also tended to occur within a similar time frame for all groups, with no difference in time to first rejection during the first year after transplant. The use of pretransplant azathioprine and conditioning with fresh or stored blood did not significantly impact on rejection. Third-party transfusions tended to improve the freedom from severe rejection in group 3 ($p = 0.08$ by Fisher's exact test; $p = 0.05$ by chi square test), but not in groups 1 or 2.

Examination of the pretransplant immunologic status of the recipient showed no relation between panel-reactive antibody and rejection. Pretransplant MLC, however, was related to the incidence of severe rejection. Patients who experienced a severe rejection within 6 months had a

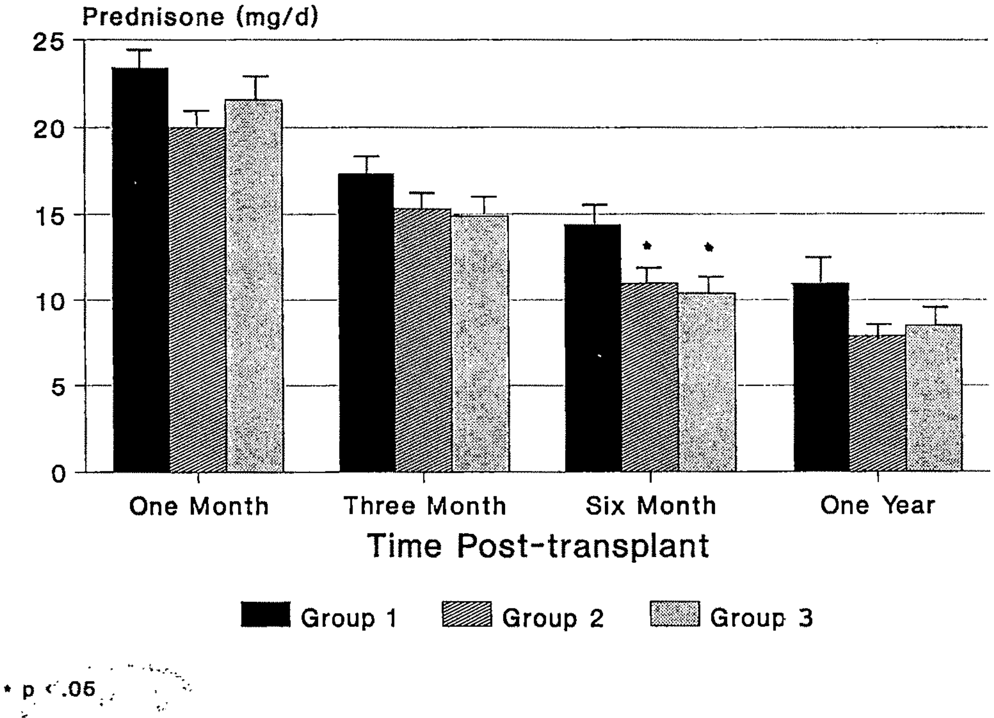


FIG. 3. Prednisone dose.

TABLE 4. *Patients with Rejection Episodes*

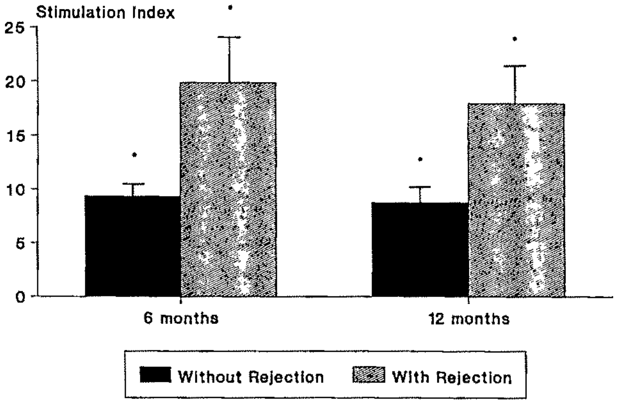
	Group 1	Group 2	Group 3	p
Rejection within first 6 months				
Total	19/34 (56%)	14/31 (45%)	11/21 (52%)	NS
Severe	13/34 (38%)	8/31 (26%)	10/21 (48%)	NS
Rejection within first yr				
Total	21/34 (61%)	14/31 (45%)	9/15 (60%)*	NS
Severe	14/34 (41%)	8/31 (26%)	9/15 (60%)*	NS
More than 1 rejection episode first yr				
Total	9/34 (26%)	4/31 (13%)	4/15 (26%)*	NS
Severe	3/34 (9%)	2/31 (6%)	2/15 (15%)*	NS
Time to first rejection (within 1 yr)	50.5 ± 17 days	32.4 ± 13 days	20.9 ± 10.4 days	NS

* Includes only patients with follow-up longer than 1 year. NS, not significant.

mean stimulation index of 19.8 ± 4, compared with 9.3 ± 1.3 for patients without severe rejection ($p < 0.05$). This relationship also was seen at 1 year with stimulation indices of 18 ± 4 *versus* 8.8 ± 1.2, respectively ($p < 0.05$) (Fig. 4). Similarly, patients with a stimulation index > 20 in their pretransplant MLC were more likely to experience severe rejection at both 6 months and 1 year ($p < 0.05$). None of five patients with a stimulation index > 50 were free from severe rejection at 1 year. Pretransplant MLC did not, however, impact on graft survival or the incidence of mild rejections.

Complications

There was concern that administration of cyclosporine before transplantation might jeopardize allograft function because of vasoconstriction and early cyclosporine toxicity. The groups treated with post-transplant *versus* pretransplant cyclosporine had a comparable incidence of early renal dysfunction that was perceived to be associated with cyclosporine therapy (Table 5). The cyclosporine level at the time of transplant (available only for group 3) did not impact on early function, nor did the route of administration (oral or intravenous) in group 2.



• p < .05

FIG. 4. Relation of pretransplant MLC to severe rejection episodes.

There were no differences in the incidence of bacterial, viral, or fungal infections except for an unexplained significantly higher incidence of CMV infection in group 2 (Table 5). One of the patients from group 2 developed life-threatening CMV infection and a lymphoproliferative disorder and subsequently died. The incidence of malignancy was low during the first year. In addition to the lymphoproliferative disorder in group 2, there were three skin malignancies (1 squamous cell and 2 basal cell carcinomas).

OKT3 Pretreatment

Six of the patients in group 3 were treated with OKT3 in the pretransplant period in addition to a single DST and pretransplant cyclosporine. There was a 33% incidence of rejection in the first 6 months in this subgroup. More importantly, without steroid pretreatment, all of

TABLE 5. *Patients With Complications in the First Year*

	Group 1	Group 2	Group 3	p
Infections				
Total	9/34 (26%)	13/31 (42%)	7/15 (47%)*	
Bacterial	7/34 (21%)	7/31 (23%)	6/15 (40%)*	NS
Viral	2/34 (6%)	8/31 (25%)	2/15 (13%)*	NS
Cytomegalovirus	(0%)	5/31 (16%)	(0%)*	NS
Fungal	1/34 (3%)	2/31 (6%)	(0%)*	<0.05
Malignancies	1/34 (3%)	3/31 (10%)	(0%)*	NS
Presumptive CsA toxicity in first 14 days	2/34 (6%)	3/31 (10%)	3/21 (14%)	NS

* Includes only patients with follow-up longer than 1 year.
NS, not significant.

the patients had moderate to severe reactions to the OKT3. One woman required intensive care after OKT3, necessitating a 3-day delay in her transplant. These patients also tended to form anti-OKT3 antibodies. Two of the six developed titers of 1:100 and 1:1,000 after the single dose, and a third patient developed a titer of 1:100 after an 11-day course of OKT3 for early rejection.

Discussion

Since the commercial availability of cyclosporine in late 1983, there has been controversy over the deliberate administration of DST in LRD renal transplant recipients.[17-19] The early benefits of DST on graft and patient survival have been markedly reduced to 3% to 9% by cyclosporine therapy[8,9] and exclusion of approximately 10% of potential donors because of sensitization has continued to occur. Conversely, experimental data have demonstrated repeatedly that cyclosporine and donor antigen, including DST, can prolong allograft survival synergistically.[11-13,20-22] Furthermore, there is the potential that immune modification through DST can decrease the need for continued immunosuppression and the severity of chronic rejection with respect to long-term graft survival in humans. Donor-specific transfusion treatment can induce the development of hyporesponsiveness of donor-specific cytotoxic T-lymphocytes[23,24] and MLC[14,25-27] in human renal allograft recipients. In one-haplotype–mismatched living related kidney recipients, Reed et al.[10] have shown that three DSTs significantly improved freedom from rejection, increased the rejection-free interval, and improved the ability to aggressively withdraw steroids when compared with random donor transfusions. Salvatierra et al.[9] recently described excellent results over the first 4 years in a protocol using DST and Minnesota antilymphoblast globulin/cyclosporine sequential therapy. In this report, DST provided a 9% benefit at 1 year and a 33% enhancement in allograft survival at 4 years over non-DST/Minnesota antilymphoblast globulin/cyclosporine-sequential therapy. The DST group also tended to have lower prednisone doses.

A persistent disadvantage of DST protocols is the occurrence of a high incidence of sensitization. The original DST protocol introduced by Salvatierra et al.[2] in 1980 consisted of three fresh whole blood transfusions at 2-week intervals. This was complicated by a 29% incidence of sensitization, resulting in elimination of these donors. Modifications of this protocol through the use of stored whole blood,[28] a single transfusion 2 weeks before transplant,[29] concurrent azathioprine,[3-5] or cyclosporine[30] has reduced the rate of sensitization to 9%, 4%, 8% to 14%, and 4%, respectively. Although these sensitized patients may successfully undergo transplantation from a different living related or cadaveric donor, this creates a significant reduction in the donor pool. Prolonged pretransplant immunosuppression also may cause bone marrow toxicity and infectious complications. In the current study, all of the patients that received a single DST and cyclosporine 24 to 48 hours before transplantation were transplanted with organs from their initially intended donor. This protocol maintained the excellent graft survival seen in our previous multiple-DST/cyclosporine groups without significantly increasing the incidence of rejection or complication. The relationship of pretransplant MLC to severe rejection episodes suggests that the single-DST/cyclosporine group may have been at a higher risk for severe rejection, yet the protocol maintained a similar profile of rejection episodes. Thus, 10% of potential donors expected to be excluded because of DST sensitization were not eliminated by this protocol and their kidneys were not lost from rejections. The burden on both the donor and recipient also was significantly reduced with regard to the pretransplant commitment to multiple transfusions, the potential risks of prolonged pretransplant immunosuppression, and costs associated with the transfusion therapy and added immunologic testing.

Concern regarding the effect of preoperative administration of intravenous cyclosporine was unfounded. There was no increase in early renal dysfunction or early cyclosporine toxicity from this treatment. Although no relation of cyclosporine level at transplant to early renal dysfunction could be demonstrated in this study, careful adjustment of cyclosporine dosage with frequent monitoring of levels seems warranted. The problem of cyclosporine toxicity has been more evident in cadaveric organs, where cyclosporine appears to potentiate the tubular damage from ischemia and storage.

Pretransplant T-cell depletion through the use of monoclonal antibodies has been shown to augment the transfusion effect induced by a single pretransplant DST.[31] The clinical application of this approach with OKT3 in six patients in this study demonstrated drawbacks associated with this therapy. There was a uniform incidence of moderate to severe reaction to the OKT3 dose, and a significant percentage of the recipients developed anti-OKT3 antibodies after treatment. Similar findings in a preliminary group of four cadaveric kidney recipients (unpublished data) confirm the adverse effects of pretransplant OKT3 dose without steroid pretreatment. This treatment did not lead to a significant reduction in early rejection and was therefore abandoned.

In summary, a single pretransplant DST combined with pretransplant initiation of a cyclosporine infusion is safe and maintains the same efficacy as previous multiple-DST/cyclosporine protocols. The burden of pretransplant conditioning is reduced, and the loss of organ donors due to sensitization is eliminated, therefore increasing the pool of living related donors. Although the major deterrents to DST have been removed, the long-term benefits of combined DST and cyclosporine administration need to be studied further.

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DISCUSSION

DR. JOHN MCDONALD (Shreveport, Louisiana): Mr. Chairman, Ladies and Gentlemen, again I am honored to be asked to discuss this paper. I would point out that Dr. Alexander consistently brings to us scholarly studies designed to answer specific and well-defined questions, and this study is no exception. The role of donor-specific blood transfusions, as you have already heard, has become unclear since the introduction of clycosporine and monoclonal antibody therapy for rejection. This study presents three sequential prospective protocols designed to approach this question. All three protocols yield similar results and, thus, the simplest and least expensive in time and money is recommended. It may be that this is indicated if you believe that blood transfusions are likely to induce a state of host adaptation that will decrease the late graft loss that I discussed in the last paper. This concept has been proposed by others, but is not addressed by the data presented in this paper. The problem with these data, I respectfully submit, relates to the fact that there is no control group of patients without transfusions or without donor-specific transfusions.

While these data were being accumulated, early results were being improved by a new, impressive protocol. For example, the previous paper presented one-haplotype graft with results that are the same as those presented in this paper, and those patients received no planned donor-specific transfusion. Thus I ask Dr. Alexander if these results lead him to believe that donor-specific transfusions are indicated at all and, if so, under what circumstances. Thank you.

DR. FRANCIS THOMAS (Greenville, North Carolina): Dr. Britt, Dr. Jones, Members and Guests, I am pleased to have the opportunity to discuss Dr. Alexander's unique clinical trial, which represents the latest extension of experimental and clinical studies his group have previously performed in single-donor-specific blood-transfused transplant recipients. His group have shown the simplicity and utility of this technique, which reduces the number of transfusions, the time on pretransplant azathioprine, and the time to transplant, while retaining, apparently, the beneficial effects of the donor-specific transfusion without sensitizing the potential recipient. The DST protocols are all variations of potentially tolerogenic recipient treatments involving administration of donor antigens to induce tolerance. Tolerance in current clinical protocols can be gauged only roughly by improved graft survival or reduced requirements for immunosuppressant drugs, both extremely laudable goals. Virtually everyone agrees tolerogenic protocols are difficult to evaluate in the related donor haplotype match because historical results are excellent with cyclosporine-A–based immunosuppression.

Our group has focused on experimental protocols for cadaveric transplantation using donor bone marrow given after transplant, which seems to be optimally effective in prolonging grafts with no immunosuppressant drugs given beyond days 3 to 5 in experimental animals and prolonged survival of the grafts. It is interesting, and I think very much to this point, that Dr. Alexander's protocol is perhaps the only current alternative to the bone marrow protocol, which would permit a conditioning regimen that would be available for use in cadaveric transplantation. My questions to Dr. Alexander focus on what our group considers the Achilles heel of the donor-specific conditioning protocols and relates, specifically, to the humoral antibody response. In our experimental animals, prolonged graft survival was achieved in every case in which anti-donor antibody did not develop. In contrast, in animals developing anti-donor antibody, whether complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity type, there was a loss of the graft, although the loss was late, in the 150-plus day range. Thus, the humoral antibody response seems to be the problem that we cannot at present block with our conditioning regimens.

The early rejections seen so prominently in the donor-specific transfusion (DST) group seem most likely to be humoral in origin on the basis of a variety of factors. The 7-day irreversible rejection was certainly most likely humoral. The single DST recipients also suffered late and repeated rejections, a problem we have associated with the humoral-type rejection.

I would like to ask Dr. Alexander if his recipients demonstrated anti-donor antibody patterns after transfusion or transplantation that were associated with rejection. Also, were any associative rejection patterns seen in historic antibody studies?

Finally, the striking association here noted between mixed lymphocyte reaction reactivity and graft rejection is provocative indeed. Dr. Alexander, have you analyzed MLR-induced lymphokine secretion profiles, such as those distinctive to the Th1 and the Th2 helper cell population, to see if this might be a factor in the high MLR reactivity? In addition, is the high MLR due to a memory cell proliferation that might reflect previous subliminal sensitization that could be detected pretransplant and, thus, averted?

In summary, I enjoyed this stimulating paper very much, and I appreciate the privilege of discussing these studies. Thank you very much.

DR. CHRIS DAVIES (Closing discussion): Dr. Britt, Dr. Jones, Members and Guests, I would like to thank Dr. McDonald and Dr. Thomas for their thoughtful questions regarding this protocol. Addressing Dr. McDonald's questions, there was no control group during the time period that received only cyclosporine without donor-specific transfusions (DST), so a comparison with cyclosporine alone could not be made. As to whether DSTs are indicated and when, I think that the point remains quite controversial. Some of the data reported by Dr. Salvatierra suggest that the quadruple-therapy–treated patients with DST there have a 1-year 9% improvement in graft survival over those not transfused. This advantage persists, with a 98% graft survival over the first 4 years, suggesting that there may be some long-term benefit, depending on the type of immunosuppression used. Dr. Reed from the University of Wisconsin reported that their donor-specific transfusion patients had a decreased requirement for prednisone, fewer rejections, and a longer rejection-free interval compared with patients in the following period who had received random transfusions. Again, it is unclear whether this is going to projected into long-term benefits regarding chronic rejection, but there are some laboratory studies, including some of our own, that suggest that cyclosporine and DST can be synergistic and can result in long-term allograft survival. Having eliminated sensitization with our current protocol, we believe that DST should continue to be studied clinically in light of its potential long-term benefits.

Addressing Dr. Thomas's questions regarding humoral antibody response, we have not measured anti-donor antibody patterns in these rejections and have no historic studies to address that. Regarding Th1 and Th2 lymphokines and memory cell proliferation, we have not looked at this. We have done posttransplant mixed lymphocyte cultures at 6 months in our cadaveric groups. The cadaveric recipients who had received DST had a 40% lower MLC to their specific donor than patients who had not received DST, suggesting induction of specific immune hyporesponsiveness in these groups. I would like to thank the Association for the privilege of participating in the presentation of this paper.

Node-negative breast cancer:

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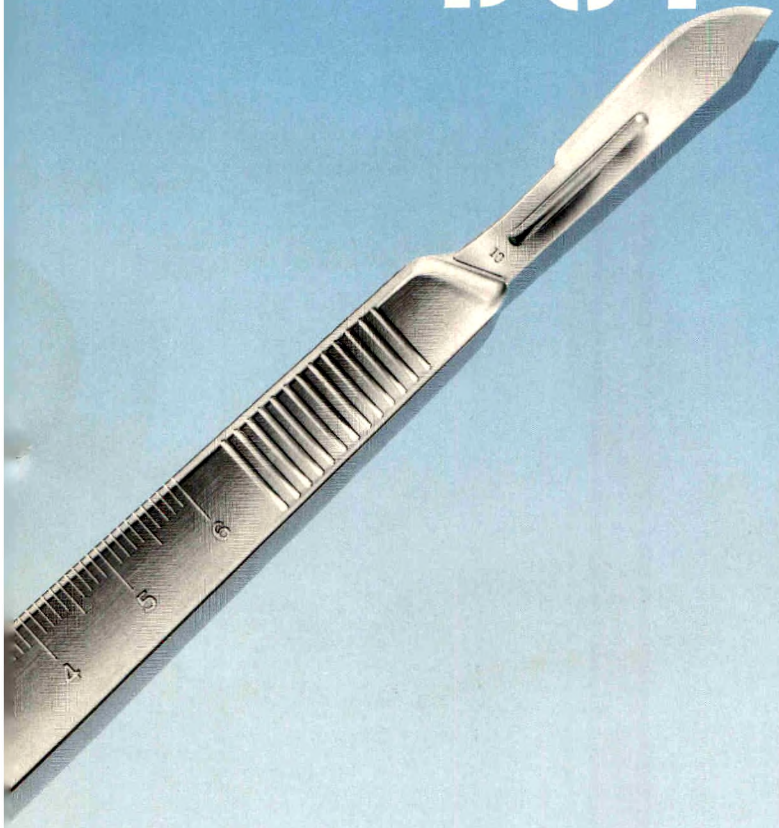

NOLVADEX delays breast cancer recurrence after surgery.

Surgery alone may not be enough to cure many patients with node-negative breast cancer—up to 30% will recur within 10 years.[1] According to the Consensus Development Conference on Early Stage Breast Cancer, "no individual patient can be assured that she has no risk of recurrence."[2] Until it becomes possible to accurately identify patients at high risk, adjuvant NOLVADEX to delay recurrence should be considered for all node-negative patients.

NOLVADEX is a rational therapy choice for node-negative patients.

The Consensus Conference states: "There is clear evidence that the rate of local and distant recurrence is decreased by both adjuvant combination cytotoxic chemotherapy and by adjuvant tamoxifen [NOLVADEX]."[2] NOLVADEX is a rational therapy choice because it is proven to delay recurrence and prolong disease-free survival in node-negative breast cancer patients.[3,4] And NOLVADEX is well-tolerated therapy, with a favorable long-term safety profile.

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NOLVADEX is effective in delaying recurrence following primary surgery in postmenopausal women with pathologic stage II breast cancer and in some women with axillary node-negative breast cancer. Insufficient data are available on the benefit in women with tumors less than 1 cm.

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INDICATIONS AND USAGE: Adjuvant Therapy: NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection or segmental mastectomy, axillary dissection, and breast irradiation in women with axillary node-negative breast cancer. Data are insufficient to predict which women are most likely to benefit and to determine if NOLVADEX provides any benefit in women with tumors less than 1 cm.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer ($T_{1\text{-}3}$, N_1, M_0). In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

The estrogen and progesterone receptor values may help to predict whether adjuvant NOLVADEX therapy is likely to be beneficial.

Therapy for Advanced Disease: NOLVADEX is effective in the treatment of metastatic breast cancer in women. In premenopausal women with metastatic breast cancer, NOLVADEX is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

CONTRAINDICATIONS: NOLVADEX is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Visual disturbance including corneal changes, cataracts and retinopathy have been reported in patients receiving NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

A small number of cases of endometrial hyperplasia and endometrial polyps have been reported in association with NOLVADEX treatment. A definitive relationship to NOLVADEX therapy has not been established.

In a single large randomized trial in Sweden of adjuvant tamoxifen 40 mg/day for 2-5 years, an increased incidence of endometrial cancer was noted. Thirteen of 931 tamoxifen treated patients versus 2 of 915 controls developed cancer of the body of the uterus [RR = 6.4 (1.4 - 28), $P < 0.01$]. However, in a review of more than 12,000 patients entered into twelve other large ongoing adjuvant studies (including NSABP B-14) in which patients have received NOLVADEX 20-40 mg/day for periods of 1-5+ years versus control, no increased incidence of cancer of the uterus was seen.

In the same Swedish trial, the incidence of second primary breast tumors was reduced in the tamoxifen arm ($P < 0.05$). In the NSABP B-14 trial in which patients were randomized to NOLVADEX 20 mg/day for 5 years versus placebo, the incidence of second primary breast cancers is also reduced.

Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX and should use barrier or non-hormonal contraceptive measures. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well-controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been reported. Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to NOLVADEX therapy.

Information for Patients: Women taking NOLVADEX should be instructed to report abnormal vaginal bleeding which should be promptly investigated.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Drug Interactions: When NOLVADEX is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

Drug/Laboratory Testing Interactions: During postmarketing surveillance, T_4 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given NOLVADEX.

In the postmarketing experience with NOLVADEX, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with preexisting hyperlipidemias.

Carcinogenesis: A conventional carcinogenesis study in rats (doses of 5, 20, and 35 mg/kg/day for up to 2 years) revealed hepatocellular carcinoma at all doses, and the incidence of these tumors was significantly greater among rats given 20 or 35 mg/kg/day (69%) than those given 5 mg/kg/day (14%). The incidence of these tumors in rats given 5 mg/kg/day (29.5 mg/m^2) was significantly greater than in controls.

In addition, preliminary data from 2 independent reports of 6-month studies in rats reveal liver tumors which in one study are classified as malignant.

Endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and although the dose was high enough to terminate pregnancy in some animals those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was obtained by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: Adverse reactions to NOLVADEX are relatively mild and rarely severe enough to require discontinuation of treatment. If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

In patients treated with NOLVADEX for metastatic breast cancer, the most frequent adverse reactions to NOLVADEX are hot flashes and nausea and/or vomiting. These may occur in up to one-fourth of patients.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache.

There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxic agents are combined with NOLVADEX.

Ovarian cysts have been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with NOLVADEX.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with NOLVADEX as compared to placebo.

In the ongoing NSABP study B-14, patients with axillary node-negative breast cancer were randomized to 5 years of NOLVADEX or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of 29 months). The incidence of hot flashes (57% v 41%), vaginal discharge (24% v 12%), and irregular menses (19% v 15%) were higher with NOLVADEX compared with placebo. The incidence of all other adverse effects

were similar in the two treatment groups with the exception of thromboembolic events (phlebitis), which although rare, were more common with NOLVADEX than with placebo.

NSABP B-14 STUDY

	No. of Patients (%)			
	NOLVADEX		Placebo	
Adverse Effect	(n = 1376)		(n = 1396)	
Hot flashes	787	(57)	566	(41)
Fluid retention	339	(25)	326	(23)
Vaginal discharge	330	(24)	160	(12)
Irregular menses	264	(19)	203	(15)
Nausea	255	(19)	235	(17)
Skin rash	180	(13)	150	(11)
Diarrhea	106	(8)	129	(9)
Vomiting	25	(2)	16	(1)
Phlebitis	15	(1)	2	(<1)
Thrombocytopenia*	10	(1)	4	(<1)
Leukopenia**	7	(1)	10	(1)

*Defined as a platelet count of $< 100{,}000/\text{mm}^3$
**Defined as a white blood cell count of $< 3000/\text{mm}^3$

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, NOLVADEX or placebo was administered for 2 years to patients following mastectomy. When compared to placebo, NOLVADEX showed a significantly higher incidence of hot flashes (19% versus 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for NOLVADEX was 10% versus 3% for placebo, an observation of borderline statistical significance.

The other adverse reactions reported equally in the ECOG study for NOLVADEX and placebo include abnormal renal function tests, fatigue, dyspnea, anorexia, cough, and abdominal cramps. A relationship of these reactions to the administration of NOLVADEX has not been demonstrated since the frequency was not significantly different from that reported in placebo treated patients.

In other adjuvant studies, Toronto and NOLVADEX Adjuvant Trial Organization (NATO), patients received either NOLVADEX or no therapy. In the Toronto study, hot flashes and nausea and/or vomiting were observed in 29% and 19% of patients, respectively, for NOLVADEX versus 1% and 0% in the untreated group. In the NATO trial, hot flashes, nausea and/or vomiting and vaginal bleeding were reported in 2.8%, 2.1% and 2.0% of patients, respectively, for NOLVADEX versus 0.2% for each in the untreated group.

The following table summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared NOLVADEX therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

	NOLVADEX All Effects Number of Patients (%)		OVARIAN ABLATION All Effects Number of Patients (%)	
Adverse Reactions*	n = 104		n = 100	
Flush	34	(32.7)	46	(46)
Amenorrhea	17	(16.3)	69	(69)
Altered Menses	13	(12.5)	5	(5)
Oligomenorrhea	9	(8.7)	1	(1)
Bone Pain	6	(5.7)	6	(6)
Menstrual Disorder	6	(5.7)	4	(4)
Nausea	5	(4.8)	4	(4)
Cough/Coughing	4	(3.8)	1	(1)
Edema	4	(3.8)	1	(1)
Fatigue	4	(3.8)	1	(1)
Musculoskeletal Pain	3	(2.8)	0	(0)
Pain	3	(2.8)	4	(4)
Ovarian Cyst(s)	3	(2.8)	2	(2)
Depression	2	(1.9)	2	(2)
Abdominal Cramps	1	(1)	2	(2)
Anorexia	1	(1)	2	(2)

*Some patients had more than one adverse reaction.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In three single agent adjuvant studies, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for 2 years (See Clinical Pharmacology). In the ongoing NSABP study B-14, one 10 mg NOLVADEX tablet is being given twice a day for 5 years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.
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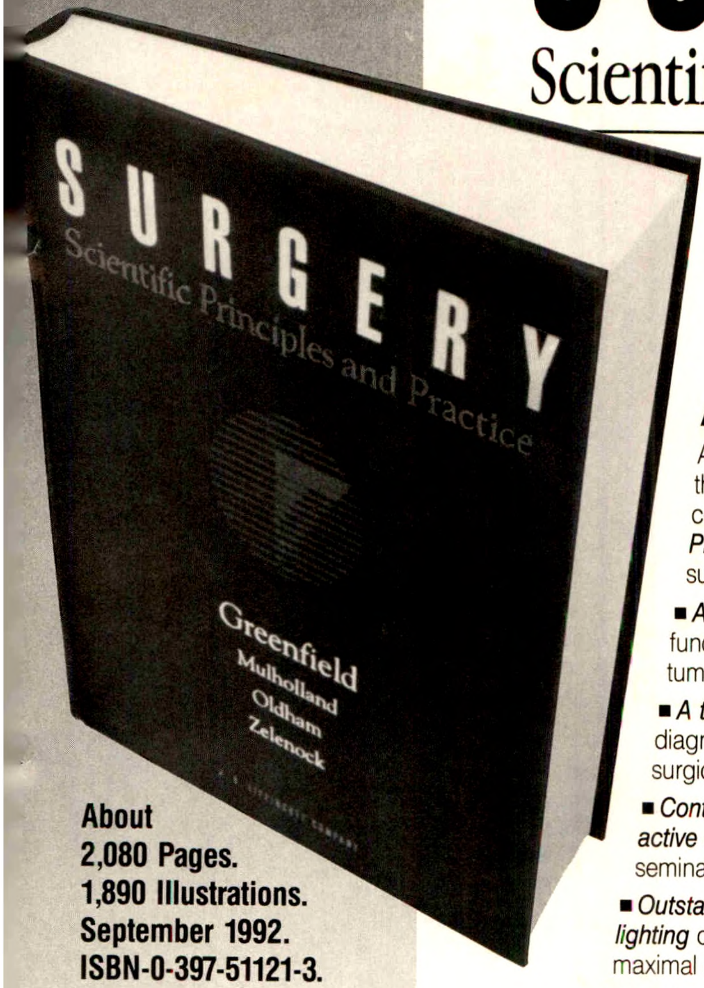

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INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus, Escherichia coli,** *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis,** *Bacteroides fragilis,** *Enterobacter* spp.,* and *Acinetobacter calcoaceticus.**
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli,** and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentration of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16%   Pain at IV injection site—3%
Thrombophlebitis—3%
Systemic Adverse Reactions
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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Management of Diabetic Midfoot Ulcers

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Diabetic midfoot ulcers are caused by bone and joint disruption that occur as a consequence of progressive peripheral neuropathy associated with this disease. This results in osseus deformities and areas of high pressure on the plantar surface of the midfoot, which cause the ulcers. These lesions are difficult to heal and frequently lead to amputation. In a series of 348 patients, 40 developed 54 midfoot ulcers. Limb preservation was achieved in 33 (61%). Wound closure was achieved in 32 (60%). The amputation rate was highest (83%) in the 10 of 12 patients with peripheral vascular disease. Successful therapy for limb preservation most often included an operation combining resection of underlying osseus deformities with debridement of affected soft tissues.

THE TREATMENT OF diabetic neuropathic ulcerations is a major challenge for surgeons. The ulcers tend to be quite resistant to traditional methods of treatment and frequently require amputation. Ulcers occur in patients with long-standing diabetes who have other severe complications related to their diabetes, including retinopathy, nephropathy, obesity, and peripheral vascular disease. This pattern of multiorgan destruction tends to make the management of the ulcers even more difficult than it might be if they were the sole manifestation of the disease process. The ulcers also create significant social and economic morbidity because approximately 10% of the United States diabetic population (5–10 million people) will be affected at some time in their lives.[1]

In the last 10 years, better understanding of the cause of the ulcerations[2-4] has led to more precise and more successful treatment, particularly of those lesions located in the forefoot.[5] Ulcers located on the heel and in the midfoot region have remained resistant to successful treatment. Heel ulcers constitute 7.5% of plantar ulcers in our diabetic population. Commonly they develop in severely debilitated and nonmobile patients. Midfoot ulcers constitute about 20% of foot ulcers and are most often found in ambulatory patients. They usually occur on the medial aspect of the foot, an area normally occupied by the arch. These individuals become severely functionally debilitated as the ulcers progress. We have reviewed our experience in the management of patients who had midfoot ulcers treated at the University of Louisville Affiliated Hospitals between 1985 and 1991.

Methods

A retrospective analysis was performed on the records of diabetic patients who had midfoot ulcers treated at the Diabetic Foot Clinic of the University of Louisville Affiliated Hospitals. Information was compiled regarding age, sex, duration of diabetes, neuropathy, retinopathy, renal function, peripheral vascular disease, smoking habits, foot ulcer history, and details of treatment. These patients were seen, examined, and treated in a clinic dedicated to the treatment of patients with diabetic neuropathic foot disorders. The care and operative procedures were supervised or performed by a single surgeon, ensuring reasonable uniformity in management.

A number of different types of treatment were attempted in an effort to heal the midfoot ulcers. The treatments ranged from total non-weight-bearing and mechanical debridement to extended periods of external fixation with orthopedic appliances. In many cases several types of treatment were applied to the same patient in an attempt to heal the wound. Total contact casting was not used because of previous problems related to patient compliance and the fact that it did not address the un-

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derlying cause of the ulcer, in other words, pressure necrosis related to anesthesia of the foot and progressive skeletal architectural disruption. Attempts to correct the skeletal architecture led to the introduction of an operation in which the contour of the arch was restored, thereby reducing the pressure on the ulcer bed.

A skin incision was made on the medial aspect of the foot above the ulcer (Fig. 1B). The base of the first metatarsal, the cuneiform, and any other bone thought to be involved in creating increased pressure were exposed (Fig. 1C). An osteotome then is used to remove the prominences and restore the arch to a relatively normal contour. A closed suction drain then was placed and the wound was closed (Fig. 1D). Necrotic tissue was excised from the ulcer bed and margins at the end of the procedure. A single preoperative dose of antibiotics of a second-generation cephalosporin was used as prophylaxis against infection. The patient was allowed limited weight bearing the next day and thereafter until the ulcer was healed and the patient fitted with protective footwear, such as extra-depth or custom-molded shoes.

Results

During the 6-year period under study, 40 patients with 54 midfoot ulcers were evaluated. The mean age of the patients was 60.2 ± 1.8 years and the average duration of diabetes before ulceration was 18.1 ± 1.6 years; 17 were women and 23 were men; 34 patients were insulin dependent.

Methods of treatment employed included non–weight-bearing and debridement, external fixation, primary amputation, and bone resection or a combination of these methods. The mean time for which the ulcers had been present before treatment in this clinic began was 212 ± 179 days. Twenty-one limbs were lost (39%). No limbs were lost within 30 days of the midfoot operation. The major reason for amputation was combined infection and peripheral vascular disease (10 of 12). The patients healed in a mean time of 129 ± 62 days after treatment was initiated. The patients were followed for a mean time of 38 ± 36 months after initial closure. Two of the ulcers recurred during that time. Additionally, two of the limbs were lost to ischemic complications approximately 2 years after the ulcers had healed. There was one complication related to resection of bone in the midfoot, a wound dehiscence 3 weeks after operation. In that patient, the ulcer healed without difficulty but the operative wound had not healed in 10 months.

Table 1 provides information regarding the status of the patients with respect to the presence or absence of

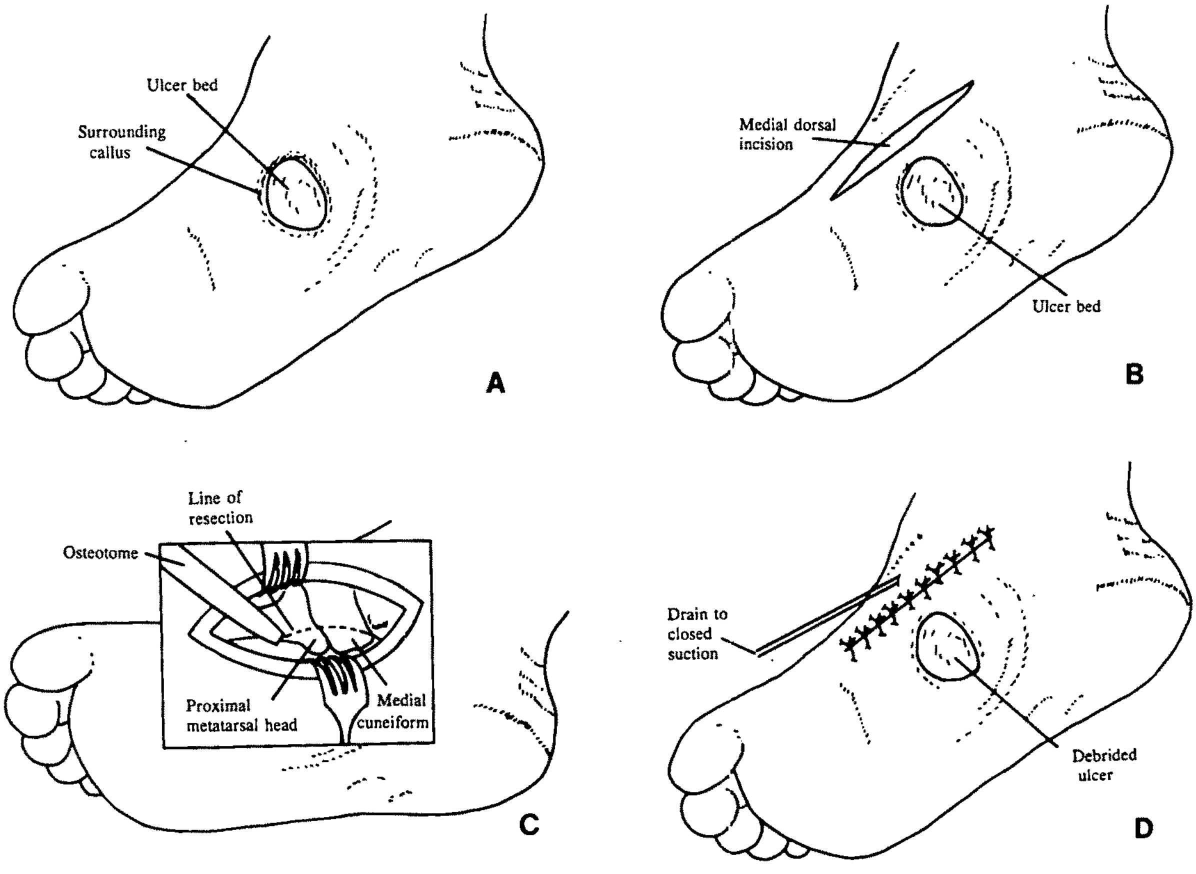

FIG. 1. (A–D) Technique of osseus resection of the midfoot ulcers.

TABLE 1. *Co-existing Conditions in Patients With Midfoot Ulcers*

	Present	Absent	Unknown	Value
Retinopathy	8	22	10	
Peripheral vascular disease	23	17	—	
Nephropathy	34	5	1	
Smoking	17	16	7	
Blood urea nitrogen (mg/dL)				30.61 ± 4.8
Creatinine (mg/dL)				2.78 ± 0.56

retinopathy, impaired renal status, peripheral vascular disease, and smoking history. Only peripheral vascular disease was related to an unfavorable outcome. Peripheral vascular disease was defined as the presence of ischemic symptoms on walking or the absence of pedal pulses. Patients without peripheral vascular disease did not suffer from claudication and had palpable pedal pulses. Impaired renal function was indicated by a serum creatinine level of more than 1.33 mg/dL or a creatinine clearance less than 1.17 mL/second.

Discussion

Previous papers from this institution have dealt with the general cause of foot ulceration in the diabetic patient.[5-7] The particular problem of midfoot ulcers has not previously been addressed as an isolated entity, yet is a common problem that causes significant hardship in a group of potentially functionally independent patients.

The primary cause of midfoot ulcers is the neuropathic degeneration of the peripheral nerves caused by metabolic disturbances and is likely exacerbated by nerve entrapment.[8] Neurologic deterioration, particularly of the pain and proprioceptive elements of the nerves, leads to hyperextension and ultimately disruption of the skeletal components of the foot. This may occur through hyperextension of the joint capsules or through avulsion of the tendons supporting the arch (Fig. 2). Disruption of the normal osseous architecture of the foot (Charcot degeneration) leads to the development of high-pressure zones on the plantar surface of the foot. The areas of high pressure ultimately lead to tissue breakdown and ulcer formation.[9-11] The process can be exacerbated by vascular insufficiency and renal impairment. It is unclear why one patient will develop ulcers on the forefoot and another in the midfoot. It may be that the midfoot lesions are related to more severe disruption that occurs with progressive disease, because midfoot lesions occur later after the onset of diabetes than forefoot ulcers (18.2 *versus* 11.4 years).

Midfoot ulcers are notably more difficult to manage successfully, as is indicated by their higher amputation rate, 39% *versus* 6.8% in forefoot ulcers. A variety of methods of treatment have been advocated, varying from total non–weight-bearing and total contact casting to triple arthrodeses and primary amputation.[12-14] A comparison of the efficacy of different treatments has been difficult because of the variable manifestations of the disease process, the lack of large series of patients treated uniformly, and until recently a poor overall understanding of the disease process itself.

The results presented herein indicate that it is possible to obtain long-term healing of midfoot ulcers and that it is possible to do so by removing the pressure points of stress, which are the proximate cause of the lesions. The results also indicate that the wounds will remain healed if properly treated and if proper care is given to the feet subsequent to the operation. It should be noted that the patients in our study are regularly followed whether they have active foot pathology or not. We have previously shown that such efforts lead to fewer ulcer recurrences. Certain technical features of the operation require comment. The location of the incision is such that the vascular supply to the foot is not disturbed. Care must be taken not to disrupt either the dorsalis pedis artery or major venous routes on the dorsum of the foot. Clearly the aim in protecting the artery is to prevent ischemia. Preservation of the vein will be of value if a later *in situ* distal revascularization is required. The use of a separate incision rather than proceeding through the ulcer bed serves two purposes. First, there is less potential for contaminating bone through a clean incision, and secondly, keeping the incision off of the plantar surface of the foot diminishes the scar formation and risk of creating another high-pressure zone subject to further ulcer formation.

One potential criticism of the operation is that joint spaces are opened and that chronic draining wounds with the potential for infection may be created. Our experience has been that if the surgical wounds are drained after op-

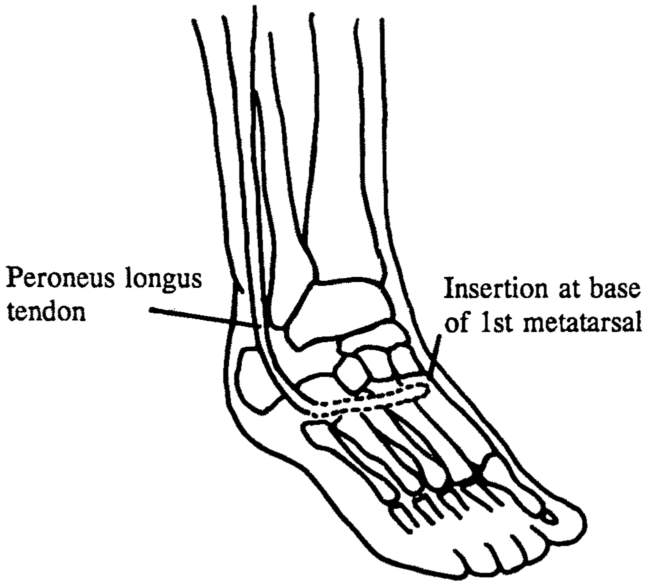

FIG. 2. Peroneus longus support of midfoot architecture.

eration, with a closed system until no further fluid is retrieved, a chronic joint fluid leak will not develop. Generally a drain is required for 48 to 96 hours after operation.

Because we minimize restrictions on weight bearing, it is important that the sutures be left in place for 3 weeks. Our early experience in operating on feet was that if major stress is applied to a wound in the first 2 weeks, disruption is common. Clearly that is unacceptable in wounds with a high risk of infection, particularly bone infection.

Finally the question must be raised as to whether the resection of bone can really be considered a permanent solution to what appears to be a continuing disruption of the skeleton of the foot. First, it is clear that sufficient bone must be removed at the operation to allow initial healing. There is no quantitative way of describing this part of the operation. As a basic rule, we visually re-create the arch of the foot (Fig. 1D). This is done by cutting along a gently curving line parallel with the inferior margin of the metatarsal shaft, ending at the base of the calcaneus. The depth of bone removed is likewise estimated by imagining a funnel-shaped cavity extending ¼ to ⅓ of the way through the foot at the level of the arch from medial to lateral.

The ultimate proof that this operation reduces pressure on the weight-bearing surfaces and thereby allows healing has not been demonstrated for these specific lesions; however, there is much evidence from other foot pressure measurements that this is indeed the case. The fact that there have been only two ulcer recurrences after this operation is reasonable proof that the method is effective. The fact that no limbs were lost as a consequence of the operation indicates its safety.

In conclusion, midfoot neuropathic ulcers represent a difficult management problem. When they present in patients with long-standing diabetes and peripheral vascular disease, the outcome will likely be an amputation. The correction of the skeletal deformity when combined with local wound care and regular postoperative foot care can lead to ulcer healing and useful extremities without prolonged periods of non–weight-bearing that may be difficult for this group of patients to tolerate.

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Discussion

Dr. J. D. Ashmore (Greenville, South Carolina): Dr. Britt, Dr. Jones, I rise and congratulate the Louisville group again for excellent work on a very difficult subject. At home, though, we see very few midfoot, but a whole lot of forefoot, ulcerations. Just recently there was an article in *JAMA* from Mt. Sinai where they did trochar bone biopsies, and most of these were forefoot ulcers. And there is a 68% incidence of osteomyelitis by culture. And I would like to ask the authors if they have cultured the bone they removed at the time of surgery and what role osteomyelitis plays in failure to heal.

Dr. Bob Ryan (Pensacola, Florida): Dr. Britt and Dr. Jones, this problem has been addressed very nicely, and I congratulate the group on identifying a specific problem, studying, and finding the cause of the problem, eliminating that problem, and the resulting healing. Yet, with any ulcer in an area where there is a compromised circulation, systemic antibiotics are of limited use, because you cannot get effective levels there; thus, a slow healing. In plastic surgery, we had a similar problem with the rare otoplasty that became infected. With adequate drainage, and removal of foreign bodies, the standard surgical care is instituted. But with the impaired circulation of the skeletonized cartilage, systemic antibiotics rarely help, and often the wound would go on to a disastrous consequence with melting away of the cartilage from the infection. This problem was solved by Rapaport and his associates and reported in the *Plastic Surgery Journal* several years ago. With the use of ionophoresis, you can drive in big doses of antibiotics, clear the infection, and achieve rapid healing with minimal deformity in the affected otoplasty. Could you speed up healing in these diabetic ulcers if you put a foot into a bucket of water with a zillion units of penicillin in it and then use ionophoresis to drive in the antibiotic? Would this speed up the healing process? Your physical therapy department has the equipment and can do this for you. Again, I want to thank you for the opportunity of discussing this paper.

Dr. Suman K. Das (Jackson, Mississippi): Dr. Britt, Dr. Jones, Members and Guests, my compliments to Dr. Polk and his co-workers for presenting such a large series of diabetic midfoot ulcers and highlighting the difficulty in managing these problem cases. They have emphasized again the basic pathologies, the neuropathy, pressure, infection, and vascular ischemic factors. They also have identified a core of patients with proximal vascular pathology who are at high risk. But we believe that diminished or lack of sensation is the most important initiating factor. Keeping that in mind, I would like to share an observation with you.

This is an x-ray of the foot of a 52-year-old unstable diabetic with midfoot large ulcers. He has recurrent ulceration, as you can see. He has good peripheral pulse. The size of the ulcer was 6 cm by 10 cm. We decided to reconstruct it with a different forum by not only bringing the skin but bringing sensation with it. That, we believe, is the primary cause. We decided to reconstruct this with a lateral arm neurovascular free flap — this is skin. This is on exploration. Debridement of the foot is here, with removal of the necrosed bone. Here we are looking at the posterior tibial artery, posterior tibial nerve. We started by doing the decompression of the posterior tibial nerve along its extent and then transferred this flap by microvascular technique, vascularizing with an end-to-side anastomosis of the posterior tibial artery, then with venae comitantes, and one of the medial plantar nerves to two of the cutaneous nerves. That is, lap of cutaneous nerve to arm and forearm. This is at the conclusion of the surgery. This is at 6 months. The interesting finding is that the sensory evaluation of this foot at 6 months, the two-point discrimination of this area and this area are between 2.5 and 4 cm, even though there is marginal improvement. But the significant finding was that the two-point discrimination of this island of skin that has been transplanted is 15 mm. This allowed the patient to be ambulatory without breaking down of the feet, even though he died a year later of massive coronary.

With that preamble, my question to you, Dr. Polk is, is there any correlation between the sensory loss and the extent and the recurrent nature of this ulcer as well as the time taken to heal this ulcer? My thanks to the Association for the privilege of discussing this paper. Thank you.

Dr. John Classen (Baltimore, Maryland): Dr. Britt, Dr. Jones, I want to thank Dr. Polk for giving me the privilege of reviewing this paper last evening, and I think he should be congratulated for his fine work and the excellent results. Such results can be obtained only in a well-organized clinic where few surgeons with great expertise work. I would like to ask Dr. Polk, under what department does this function? What disciplines make up the staff of this clinic? For the past 40 years I have had a dynamic interest in neurotropic arthropathy with ulceration. In 1966, as a new member, I gave my first paper here on that subject. My partner, George Finney, wanted to discuss what we should talk about, and I suggested Dodd's posterior perforator syndrome or neurotropic arthropathy. Because the patients came mostly from Hopkins clinic, he suggested I talk to Dr. Blaylock. I went in Dr. Blaylock's office, and he said, "Nobody wants to hear about veins; I'd talk about the other thing, but I'm not sure they will know what you're talking about." I gave the paper just before the banquet, and I am not sure anybody did know what I was talking about. But in 1966 I pointed out that rocker ulcers of the midfoot were the most challenging. An aggressive surgical approach might lead to more amputations than did the natural history of the disease. I think except in the hands of a skilled few, this may be right. I concur with Dr. Polk's concept of the pathophysiology leading to destruction of the midfoot, but not with the concept of developing the ulcer through pure necrosis. I believe that these ulcers develop from bits of cartilage and bone breaking through, migrating through the plantar fascia subcutaneous skin as the joint moves back and forth. The fact that simple casting heals most of the ulcers rather rapidly, I believe, substantiates this. This slide shows a classical plantar ulcer that healed within 6 weeks. Obviously, this will recur. The authors point out that this is not proper treatment because it does not correct the basic defect. I think if you cast this long enough, eventually this will fuse and cure the problem. Unfortunately, most of us do not have that patience. More recently we have come to the conclusion that you can treat this process in two ways. Certainly removing the bone is effective, as well documented today by Dr. Polk and his group, but so is fusing this foot. And more recently we have been reconstructing; as you can see, there is a graft placed on the lateral side of that foot that healed at first, then has gone in, then positioned properly, fused with those screws, and there is the result. This patient has gone 2 to 3 years without any recurrence of his ulcer, and we have had several others with equal follow-up. I might say that my experience over the 40 years during which I have averaged probably 10 patients — not of this type, but of the forefoot — every day in the office has been that it is infrequent to find peripheral arterial insufficiency in these people. I have seen people develop arterial insufficiency after they have had the ulcer for a long time. I want to congratulate the authors again for this fine work, and I will be looking forward to further follow-up reports. I thank you.

Dr. George Johnson (Chapel Hill, North Carolina): Dr. Polk and his group continue to see things I have been looking at for a long time but never saw. This is a very relevant paper for those caring for these unfortunate patients. So often we attempt to achieve success with operations designed to preserve rather than to eradicate all the diseased tissue. These attempts often end up with repeated operations and long-term morbidity of the patient. The procedure they espouse, however, preserves normal soft tissue and radically removes the osteomyelitic bone.

I have several questions. How did they use antibiotics? Were they organ-specific or broad-spectrum antibiotics used as shotgun therapy? Did they keep these patients on long-term antibiotics? What was the average hospital time? Some of ours stay in the hospital, it seems, for long periods of time. It took an average of 212 days for the wound to heal in their patients. How much of this time was spent in the hospital?

Although revascularization was not mentioned in the abstract, I was delighted to see they emphasized its importance in the presentation. We often see attempts to treat these patients with an inadequate blood supply. I have tried to categorize our patients similar to the author's method. Unfortunately, the many variables prevented me from making definitive conclusions, and all my efforts were for naught. I appreciate Dr. Polk attempting to separate a subgroup of these patients with specific recommendations. Thank you very much.

Dr. T. Jeffery Wieman (Closing discussion): Dr. Britt, Dr. Jones, first of all, I would like to thank all of the discussants. I honestly had not anticipated that at this hour, and particularly on this subject, but I am very appreciative of everyone's interest.

First of all, Dr. Ashmore, with respect to osteomyelitis, without a biopsy, it is clinically extremely difficult to determine whether the process that is observed in these individuals is infectious or simply osteoarthritic in nature. And if we have evidence that the patients have previously had a regional or systemic infection or if there is evidence on x-ray that osteomyelitis is present, we certainly do culture the bone. We have not done so for every patient in this study, although I think one could make a strong case for that.

Dr. Ryan, your comments and thoughts are certainly interesting and provoking. We would totally agree that systemic antibiotics can be ineffective in the person with distal peripheral vascular insufficiency. We have not used ionophoresis, but what I have begun to use is antibiotic beads. I cannot give you any results, but we do recognize the problem and are working along those lines.

Dr. Das, that was a very interesting set of photographs and concept. And in principle, we would agree with your ideas regarding the origination of the problem in terms of neurologic or the insensate nature leading to bone and joint distraction and ultimate ulceration. There are a couple of interesting observations in this area, one by Dr. Lee Dellon, who has studied nerve conduction in these patients and who has theorized, based on both experimental and clinical work, that there is not only a metabolic component to the neuropathy but, in addition, a nerve entrapment syndrome that, when combined with the metabolic neuropathy, leads to sufficient anesthesia to allow the ulceration to develop. Anecdotally, we have, in the course of operating on these patients, decompressed the number of nerves, the posterior tibial nerve in particular, and found that indeed the patients have regained a significant amount of sensation. We are continuing to pursue that course and are actually beginning a trial of nerve decompression. In looking at your photographs, I think it is possible that in the course of your transplant, you have, in effect, decompressed, to some extent, the sensory nerves, and that may be a contributory element. We have hopes that that will allow the patients to regain or retain enough sensation, much like in the median nerve entrapment syndrome, to allow preservation of function and prevention of ulceration.

Dr. Classen, again, we are very much appreciative of your comments, and what an enormous experience. I only hope that I can have that kind of reflection at such a stage in my career. I have to admit that I had not thought about fragments of bone and cartilage. We have not observed those in our own series, but have not specifically looked for them. Our clinic is developed within the department of general surgery and it is staffed by general surgeons, general surgical residents, and fellows. We, in addition, certainly use a good number of ancillary personnel and, when appropriate, we certainly do not hesitate to call on our colleagues who have other special skills.

Dr. Johnson, regarding antibiotics, again, we use shotguns. Most of the organisms that are found fall within the range of what we use. I will say only one other thing about that: we do not use systemic aminoglycosides. The risk of renal injury and perhaps ototoxicity in these patients is quite real, and I do not think it is worth it. How long do we use them? If the patient has not been infected, we use them only in the perioperative period. Of course, if there is evidence of ongoing infection, I may use them for a prolonged period, up to a month or 6 weeks. Regarding hospital time, the average hospital time for this group of patients in whom the operation was carried out electively is between 24 and 72 hours. We try to keep the patients until their drains are pulled, no longer. Because of the technique we use, we have very loose limits on their mobility, which I think is extremely important for this group of patients, many of whom are obese, who spend a great deal of time going to other doctors besides us, not to mention dialysis, ophthalmologists, and this type of thing. As for the question involving revascularization, we would consider it paramount. You cannot heal, as was demonstrated by poor results, those patients who have no blood supply. We find that, if the patients do not have good blood supply initially, we want them revascularized before our attempts to reconstruct the arch. If not, we have occasionally proceeded, generally with poor results.

One final general comment. It stems from something that Dr. van Heerden said this morning and that was echoed by Dr. Thompson. In beginning this study, we looked through the literature. And in spite of the fact that this is an extraordinarily common disease, it was very difficult to find enough references to fill one page, let alone the 1500. I think perhaps that is one justification for looking into this kind of thing.

One comment to Dr. Polk, and that is that our association now has gone on for over 20 years. I think that his stimulation itself has been exciting enough that I do not mind looking into more mundane problems occasionally. My life stays sufficiently excited as it is. I would like to thank the Society, Dr. Britt, and Dr. Jones for the opportunity to participate.

Is Type II Diabetes Mellitus (NIDDM) a Surgical Disease?

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Since February 1, 1980, 515 morbidly obese patients have undergone the Greenville gastric bypass (GGB) operation. Of these, 212 (41.2%) were euglycemic, 288 (55.9%) were either diabetic or had glucose intolerance, and 15 (2.9%) were unable to complete the evaluation. After the operation, only 30 (5.8%) patients remained diabetic (and 20 of these improved), 457 (88.7%) became and have remained euglycemic, and inadequate data prevented classification of the other 28 (5.4%). The patients who failed to return to normal glucose values were older and their diabetes was of longer duration than those who did. The effect of the GGB was not only limited to the correction of abnormal glucose levels. The GGB also corrected the abnormal levels of fasting insulin and glycosylated hemoglobin in a cohort of 52 consecutive severely obese patients with non–insulin-dependent diabetes. The GGB effectively controls weight. If morbid obesity is defined as 100 pounds over ideal body weight, 89% of the patients are no longer "morbidly" obese within 2 years. In most patients, the control of the weight has been well maintained during the 11 years of follow-up; most of the upward creep in weight of 20.8% between 24 and 132 months was from the 49 (9.5%) patients who had staple line breakdowns between the large and small gastric pouches. Non–insulin-dependent diabetes, previously considered a chronic unrelenting disease, can be controlled in the severely obese by the gastric bypass. Whether the correction of glucose metabolism affects the complications of diabetes is unknown. Whether the gastric bypass should be considered for patients with advanced non–insulin-dependent diabetes but who are not severely obese deserves consideration. The GGB has an unacceptably high rate of staple line failure. Accordingly, the authors have recently changed their procedure to one that divides the stomach rather than partitions it with staples.

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DIABETES MELLITUS IS one of our most serious diseases. It accelerates the development of atherosclerosis, doubles the risk for stroke, and increases the risk of heart attacks twofold to threefold. Through its damage to the microvasculature, diabetes produces retinopathies, blindness, nephropathy, and neuropathy. In addition, there are broader systemic effects, such as the lessening of resistance to infection. The economic impact of the disease is enormous; in 1985 it was estimated to be $4 billion and may well be twice that high given the inflation in health care costs. Although the exact prevalence is unknown, the usual estimate is that 10 million Americans have the disease and, of these, 1.25 million take insulin, 1 to 1.5 million are on oral antidiabetic agents, and another two to three million are being managed by diet alone. Many remain undiagnosed. The disease is generally classified into two groups: type I diabetes or insulin-dependent diabetes, which afflicts about 200,000 to 300,000, and the far more common type II diabetes or non–insulin-dependent diabetes mellitus (NIDDM), which accounts for more than 95% of the cases.[1]

The basis for the current treatment of NIDDM is the maintenance of euglycemia and normal insulin levels. This "control of the diabetes" is considered the best approach to prevent the acute and chronic complications of diabetes and to ameliorate those changes that are already present.[2] Unfortunately, euglycemia cannot be

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achieved in most patients with NIDDM because they are usually overweight and resistant to dietary controls. In fact, their excess weight is a major factor in precipitating the overt diabetes, especially in those predisposed by heredity.[3] In Rochester, Minnesota,[4] 59% of cases of diabetes were diagnosed among men and women with a body mass index (BMI) greater than 28.3 kg/m^2, and in the Nurses' Health Study,[5] 61% of the diabetic women aged 30 to 64 had BMIs of 29 kg/m^2 or more. Among these obese women, 94% of NIDDM prevalence was attributed to obesity.

Over the last 11 years, we have treated 515 severely obese patients, most of whom demonstrated abnormalities of glucose and insulin metabolism, with surgery to control their weight. The operation, the Greenville gastric bypass (GGB), limits intake by the fashioning of a small gastric pouch, delays gastric emptying with a small outlet, and bypasses the foregut with a Roux-en-Y anastomosis. The procedure is effective: in addition to inducing long-term weight loss, it helps in the control of hypertension and returns many of those handicapped by severe obesity to functional effectiveness.

Four years ago, we[6] reported that the GGB operation restored some of the severely obese patients with NIDDM to euglycemia. This article is a report of our continued studies of the effect of the procedure on the glucose and insulin metabolism of these patients.

Materials and Methods: Clinical Studies

From February 1, 1980 to August 1, 1991, 515 consecutive morbidly obese patients (each exceeding their ideal body weight by 100 pounds or more) underwent the standardized GGB.

Demographic Data

The 515 patients included 359 white and 79 black women as well as 64 white and 13 black men. Of the group, 360 were married, 44 were divorced, 83 were single, 18 were separated, and 10 were widows. The job status survey showed that 324 were employed and 191 were not.

Diabetic Status

The state of the diabetes was defined in accordance with the standards of the National Diabetes Data Group (Table 1).7 Of the 515 patients, 500 completed oral glucose tolerance tests; in 15 (2.9%), a lack of full data (because of a missing or suspicious sample in the glucose tolerance test curve) prevented accurate assessment. Of the 500 evaluable patients, 212 (41.2%) were classified as normal, and 288 (55.9%) demonstrated abnormal glucose metabolism. Of the 288 patients with abnormal glucose metabolism, 137 (26.6%) were classified as NIDDM, 63 (12.2%) as glucose impaired, and 88 (17.1%) as undefined.

TABLE 1. *Diagnostic Criteria for Diabetes Mellitus and Impaired Glucose Tolerance as Defined by the National Diabetes Data Group**

Non-Insulin-dependent Diabetes Mellitus

Criteria for diabetes mellitus: Diagnosis of diabetes mellitus in nonpregnant adults should be restricted to those who have one of the following:

1. A random plasma glucose level of 200 mg/dL or greater plus classic signs and symptoms of diabetes mellitus, including polydipsia, polyuria, polyphagia, and weight loss.
2. A fasting plasma glucose level of 140 mg/dL or greater on at least two occasions.
3. A fasting plasma glucose level of less than 140 mg/dL plus sustained elevated plasma glucose levels during at least two oral glucose tolerance tests. The 2-hr sample and at least one other between 0 and 2 hr after the 75-g glucose dose should be 200 mg/dL or greater. Oral glucose tolerance testing is not necessary if the patient has a fasting plasma glucose level of 140 mg/dL or greater.

Impaired Glucose Tolerance

Criteria for impaired glucose tolerance: Diagnosis of impaired glucose tolerance in nonpregnant adults should be restricted to those who have all of the following:

1. A fasting plasma glucose level of less than 140 mg/dL.
2. A 2-hr oral glucose tolerance test plasma glucose level between 140 and 200 mg/dL.
3. An intervening oral glucose tolerance test plasma glucose value of 20 mg/dL or greater.

* We have added another category, "undefined": Those patients with abnormal plasma glucose values but who do not fit into either of the above two groups.

Patient Selection and Eligibility

Patients of either sex were considered eligible for inclusion if they met the following criteria: (1) ages between 18 and 65 years (although an exception was made for a girl of 16); (2) severely obese, in other words, they exceeded their ideal body weight as given in the midpoint of the 1983 Metropolitan Life Insurance Tables by 100 pounds or more; (3) suitable operative risks after evaluation of their physical and emotional status; (4) capable of understanding the operation and the postoperative consequences and instructions; (5) agreement to long-term follow-up; (6) informed consent; and (7) funding for the surgery and the various required tests. Patients were excluded during the course of the evaluation if they (1) were not sufficiently obese; (2) had a history of alcohol or substance abuse within the last 5 years; (3) had a history of severe psychiatric dysfunction, especially evidence of suicidal attempts, serious depression, or paranoia; and (4) had inappropriate expectations of the surgery in spite of counseling, and met strong continued opposition by other family members.

Preoperative Evaluation

We have continued to decrease the intensity of our preoperative evaluation over the 11 years of the study with the elimination of those tests, such as levels of trace elements, that have produced too few significant abnormal levels to warrant the effort and the expense. Our current approach includes the following examinations:

1. complete history and physical examination with measurement of waist-to-hip ratios, body mass index (kg/m^2), and vital signs
2. routine admission studies, including complete blood count, SMA-12, electrolytes, vitamin B_{12} level, thyroid-stimulating hormone, prothrombin time, partial thromboplastin time, urinalysis, posteroanterior and lateral chest roentgenograms, electrocardiogram
3. glucose tolerance test
4. specialized tests for the evaluation of surgical risk, including pulmonary function testing and determination of anergy with skin tests (PPD, mumps, and fungus)
5. immersion hydrostatic weighing to determine body composition
6. the evaluation of mental health, physical function, and role function with a standardized interview with the project psychologist or psychiatrist

This description of our method is not intended to serve as a prescription for others treating severe obesity. We recognize that our evaluation, carried out to support our various studies, is more detailed and rigorous than would be needed in daily bariatric surgical practice. Even so, our patients have only rarely complained about the extent of the workup. It is our impression that most patients find the attention comforting rather than an annoyance.

The Surgical Intervention: The Greenville Gastric Bypass

We have carried out the identical operation, shown in Figure 1, as described by Pories,[8] a variation of the procedure originally described by Mason and Ito,[9] since February 1, 1980. Details in bariatric surgery often mean the difference between success and failure. The operation is technically demanding and the administration of the general anesthesia in these often huge individuals is a challenge. In those patients with marginal cardiopulmonary function, the insertion of a Swan-Ganz catheter and preoperative stabilization in an intensive care unit can reduce operative risk. A Gomez self-retaining retractor or one of the other retracting mechanisms that is clamped to the operating table is essential to achieve adequate exposure. The abdomen is entered through a high midline incision that extends around the umbilicus in most cases. If the exploration does not demonstrate contraindications to the procedure, the dissection around the upper portion of the stomach is begun by inserting the index finger gently into the angle at the cardia to the left of the esophagus. At this point there is a weak, thin area of the posterior peritoneum that is easily entered by the dissecting finger. The dissection is gently continued behind the esophagus and cardia. The channel is complete when the finger is brought out, not at the right side of the esophagus, but just below the first arcade of branches from the left gastric artery about 2.3 to 3.0 cm below the cardia. A large Malecot catheter, from which the bulbous end has been cut, is used to pull one limb of the TA-90 four-staple-line device through the passage. A proximal pouch measuring 4 cm in width and 1.5 cm in height is then separated from the stomach by firing the staples. A figure-of-eight 3–0 polypropylene suture is placed at the end of the staple line to close the ends securely and to serve as guy sutures during the anastomosis. The stomach is then divided by cutting between the two paired lines of staples, and both staple lines are then oversewn with 3–0 absorbable suture. (The division of the stomach is new: the partitioning of the stomachs of the 515 patients reported in this report was accomplished with the stapler alone. The high incidence of staple line failure and the success of gastric division for revisions of failed gastric bypasses has convinced us that division is the better approach and, accordingly, on October 25, 1991, we changed our protocol, altering our procedure for the first time in over 11 years.) The jejunum is divided at the apex of the first or second arcade (depending on which provides a longer Roux-en-Y limb), about 40 cm from the ligament of Treitz, with a cutting stapling device, and the distal end is then sutured to the gastric pouch. The anastomosis is sewn to fit snugly around a 0.8-cm Salem sump tube in two layers with continuous 3–0 poly-

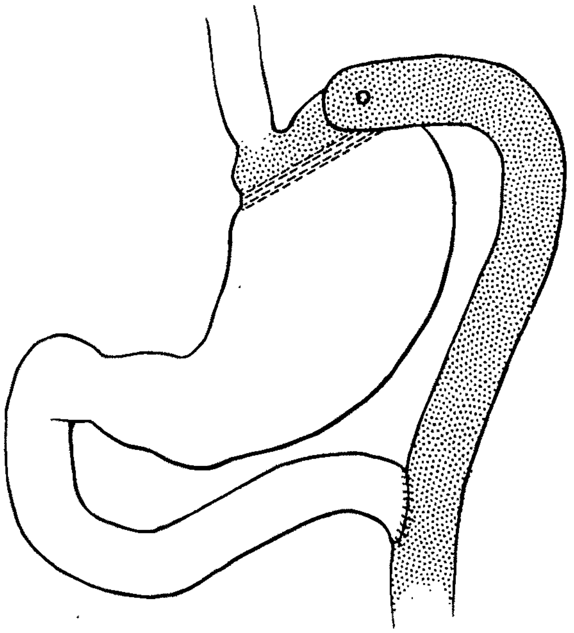

FIG. 1. The Greenville gastric bypass. The operation creates a proximal gastric pouch of 20–30 mL by the placement of a transverse double row of staples that empties into a 40-cm jejunal limb through an 8-mm gastroenterostomy. The high rate of staple line failure (9.5%) has led us recently to divide the stomach between the two staple lines.

propylene suture. The entero-enterostomy is then completed by joining the proximal jejunum end-to-side to the distal jejunum with the cutting and the TA 55 staplers. It is important to fasten the Roux loop to the mesocolon with several sutures to prevent an internal hernia and to oversew the bleeders inside the entero-enterostomy before closing the intestine. The abdomen is closed with a running, double-stranded, 1-absorbable monofilament suture. The skin is closed with skin staples without a subcutaneous suture line. The operation usually can be performed in 1 to 2 hours; blood loss rarely exceeds 300 mL.

Postoperative Care

In general, the postoperative care of bariatric patients resembles that after standard abdominal surgery in high-risk patients and therefore will not be described in detail except to emphasize the need for prophylactic antibiotics, careful monitoring of vital signs, fluid balance, and glucose metabolism, and the requirement for appropriate furniture and equipment to manage these massive patients. The first 24 hours are particularly critical because of the serious consequences of a leak or intra-abdominal infection in the morbidly obese. If the pulse remains over 120 for more than 4 hours without an evident reason, if there is a rise in body temperature to over 39 C (102 F), or if the patient looks ill in spite of normal signs, prompt emergency exploration and the addition of other antibiotics may be needed. Examinations with the swallow of radiopaque materials to demonstrate leaks are not reliable and should not be used as a reason for failure to re-explore. Neglect of a perforation or intra-abdominal infection is associated with a high mortality rate. Patients generally spend the first night in the critical care unit or a monitored ward bed for close observation and then spend the rest of their hospital stay (usually a total of 5 to 6 days) on surgical wards. Nasogastric tubes are usually removed on the third day. When the patients pass flatus, they are begun on water at 1 oz/hour, followed by the addition of a high-protein fluid preparation, half-strength on the next day, and full-strength on the day of discharge. Patients are maintained on the full-strength preparation for 2 weeks and then advanced slowly to a regular diet.

Follow-up

Follow-up has been rigorous. Return visits are timed weekly for the first month, then every third month for a year, and for every 6 months for continuing follow-up. Over the 11 years we have maintained follow-up with all but 17 of the 515 patients (96.7%).

Biopsies for Studies of Insulin Action

A 10-mL sample of venous blood and biopsies of fat, liver, muscle, and pancreas were obtained in several cohorts of patients in accordance with protocols approved by the institutional review boards of the East Carolina University School of Medicine and the Pitt County Memorial Hospital. The blood and cold steel biopsies were obtained as soon as the abdomen was opened and after a thorough exploration showed no contraindications to the biopsies. The specimens of fat, measuring about 3 × 3 × 1 cm, were removed from (1) subcutaneous fat, (2) properitoneal fat, and (3) omental fat. The liver samples, measuring 2 × 2 × 3 cm, were usually obtained from the leading edge of the left lobe, but sometimes from the right, depending on the exposure. Hemostasis and closure of the defect were obtained with serosal running sutures of 3–0 absorbable braided suture. The strips of rectus muscle, measuring 1 × 0.5 × 3 cm were obtained by blunt elevation of the fibers from the muscle bed, clamping these into a specially designed clamp to maintain their stretch, and transecting the fibers proximally and distally to the clamp. Pancreatic biopsies have only been done recently. These samples, measuring 0.3 × 0.3 × 0.3 cm, were removed from the inferior side of the body of the pancreas after incising the peritoneum at the junction of the mesocolon and the posterior peritoneum. After the removal of the specimen, the pancreatic capsule was closed with one suture of 3–0 monofilament absorbable suture and covered with the peritoneum closed with the same material. To our knowledge, and after continuing rigorous review of our records, we know of no instance in which any of the biopsies produced a complication.

Our methods for isolating insulin-responsive human hepatocytes,[10] human skeletal muscle,[11] and human adipocytes[12] have been previously described. Results from these *in vitro* studies have been recently reviewed by Caro and his associates.[13]

Results

Control of Weight

Weight reduction in these patients has been dramatic and well maintained over the 132 months of follow-up. Table 2 presents the weight loss of all 515 patients who have undergone the GGB in time intervals after surgery, in mean weight in pounds, in mean percentage of excess weight loss, and in mean percentage of ideal body weight as indicated by the 1983 Metropolitan Life Insurance Tables. If severe obesity is defined as 100 pounds over ideal weight, 89% of the patients are no longer "morbidly" obese within 2 years. Figure 2 demonstrates that there is some weight gain between 24 and 132 months (from a mean of 183 to 221 pounds or 20.8%), reflecting those 49 (9.5%) patients who had staple line breakdowns and others who learned to "outeat" their pouches with high-calorie liquids or continued snacking.

"Reversal" of Diabetes

Table 3 shows that of the 500 severely obese patients who completed the oral glucose tolerance test and un-

TABLE 2. *Weight Loss History With Greenville Gastric Bypass After 11 Years' Follow-up*

Time	N*	Weight (lb) Mean (Range)	% Excess Weight Lost Mean (Range)	% of Ideal Body Weight Mean (Range)
Before operation	515	296 (196–565)	0	216 (140–327)
3 mo	474	239 (124–490)	37 (6–103)	174 (97–307)
6 mo	470	211 (100–441)	55 (0–137)	154 (73–282)
12 mo	439	187 (104–466)	71 (13–124)	136 (85–268)
24 mo	348	183 (105–367)	72 (9–116)	134 (88–248)
36 mo	274	197 (112–411)	65 (−10–114)	142 (88–256)
48 mo	248	199 (114–413)	61 (−22–112)	145 (87–253)
60 mo	236	201 (107–428)	60 (−15–118)	147 (86–263)
72 mo	201	203 (121–399)	58 (8–133)	148 (79–270)
84 mo	172	203 (113–378)	59 (−10–109)	150 (94–273)
96 mo	132	204 (130–357)	56 (8–97)	153 (103–259)
108 mo	97	205 (125–392)	55 (6–95)	151 (104–276)
120 mo	44	198 (130–350)	56 (9–106)	149 (97–226)
132 mo	11	221 (174–346)	42 (29–58)	162 (139–212)

* No. of patients with recorded weight within each time interval ranging from ±15 days at 3 mo after operation to ±5 mo at 11 yr after operation.

derwent the GGB, 288 (57.6%) were either diabetic (137) or had glucose intolerance (151). Of the 137 patients with NIDDM, 107 (78.1%) went into clinical remission, 20 (14.6%) improved, and eight (5.8%) demonstrated no change. Two patients (1.5%) died in the perioperative period and could not be evaluated. Of the 151 patients who were not classified as NIDDM but who had abnormal preoperative glucose values, 13 had no follow-up glucose data. Of the 138 who did, all but two (98.6%) maintained normal fasting blood glucose levels. The two (1.2%) who did not return to euglycemia progressed to NIDDM.

Before surgery, 24 received insulin and another 25 were under treatment with oral antidiabetic agents. After surgery, three were subsequently placed on insulin and 11 on the oral medications.

The effect of the GGB is not limited to glucose levels alone. Table 4 demonstrates that the GGB corrected the abnormal levels of fasting blood glucose, fasting insulin, and glycosylated hemoglobin in a cohort of 52 consecutive severely obese patients with NIDDM.

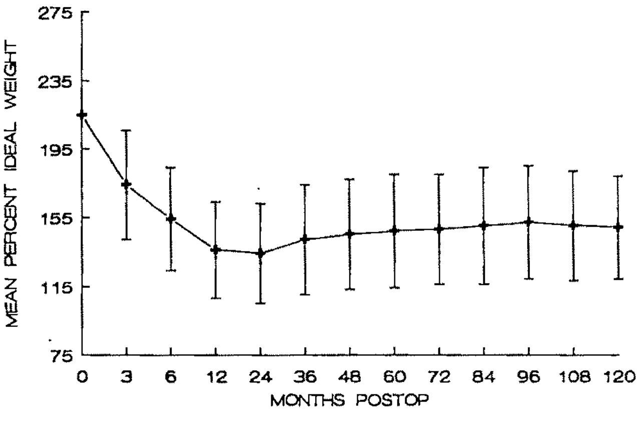

FIG. 2. Weight loss induced by the gastric bypass is well maintained over the 132 months of observation. The modest upward creep by the 11th year is primarily caused by the failure of the gastric staple lines.

The 28 NIDDM patients who did not go into complete remission and the two glucose-impaired patients who progressed to NIDDM were examined in detail. Factors that may be associated with these failures include four patients with staple line breakdowns, two patients with gastric outlet dilatation, eight patients with rising weight that may be indicative of dietary indiscretion or undiagnosed staple breakdown, one patient with Hodgkin's disease, and one patient with severe arthritis and steroid-associated weight gain, leaving 15 patients without discernible risk factors.

Patients with good glucose control were about 8 years younger (41.9 ± 1.9 *versus* 49.6 ± 2.8 years), and their diabetes was of far shorter duration (1.75 ± 0.69 *versus* 8.79 ± 2.8 years) than those patients who had poor glucose control.

The level of preoperative fasting glucose also determines the degree of postoperative control, as shown in Figure 3. The patients with the higher postoperative glucose values experienced greater drops in fasting blood sugar than their

TABLE 3. *The Control of NIDDM With the Gastric Bypass (n = 515)*

	Before Operation	After Operation
Euglycemic	212 (41.2%)	457 (88.7%)
Hyperglycemic	288 (55.9%)	30 (5.8%)
Non–insulin-dependent diabetes mellitus	137 (26.6%)	
Impaired glucose tolerance	63 (12.2%)	
Undefined, but abnormal	88 (17.1%)	
Inadequate data	15 (2.9%)	28 (5.4%)

NIDDM, non–insulin-dependent diabetes mellitus.

TABLE 4. *The Correction of Abnormal Glucose Metabolism After the Gastric Bypass (n = 52)*

	Before Operation	1 Yr After Operation
Average weight (kg)	120.1 ± 4.4	83.0 ± 3.3
Fasting blood glucose (mg/dL)	212.3 ± 20.8	117.3 ± 11.5
Fasting insulin (μM/mL)	44.8 ± 4.1	13.4 ± 2.0
HbA1c	10.8 ± 0.6	6.4 ± 0.2

more normal counterparts, but leveled out at levels that were still abnormal.

The improvements in insulin levels, glycosylated hemoglobin (HbA1c), and glucose levels do not parallel each other consistently. In contrast to the insulin levels that fall predictably after gastric bypass (Fig. 4), the levels of HbA1c (Fig. 5) and fasting blood sugar (Fig. 6) on the same group of patients show a much wider scatter. The reasons for this unexpected difference in the behavior of these diabetic indices is not clear.

The glucose tolerance curves and fasting insulin levels were compared in 117 lean controls, 85 nondiabetic obese, 39 glucose-impaired obese, 29 NIDDM obese with fasting blood sugar < 140 mg/dL, and 25 NIDDM obese with fasting blood sugar > 140 mg/dL. The data, shown in Figures 7 and 8, suggest that insulin production continues to rise with increasing insulin resistance until, finally, the beta cells fail to reach effective insulin production on demand and, as a consequence, blood glucose levels rise out of control. In short, the progression of the two diseases, NIDDM and obesity, parallel each other. The diabetes, these data suggest, appears to be due to ever-increasing insulin resistance and the eventual failure of the pancreas to meet the ever higher demand for insulin production. In a way, type II diabetes mellitus, at its most severe and terminal point, resembles type 1 diabetes, with inadequate insulin production.

Control of Hypertension

The GGB favorably affected hypertension. Of the 515 patients, 301 (58.4%) were hypertensive before the operation and, of these, 169 (56.1%) were on antihypertensive medication. After the GGB, 96 of the 301 (31.9%) remained hypertensive, and 88 (29.2%) were maintained on antihypertensive therapy.

Perioperative and Late Complications

The perioperative mortality rate was 1.2%, in other words, six of 515 patients died within 30 days after their operation or during their first hospitalization, a low rate in view of the fact that 47 (9.1%) of these patients in the series were, in addition to being severely obese, also in cardiopulmonary failure before surgery. As demonstrated in Table 5, 83% of the perioperative deaths were of sepsis.

There were 17 late deaths, of which 7 (41.1%) were related to emotional problems: three were suicides, two died of cirrhosis due to alcohol abuse, and two died of self-imposed malnutrition. Another three, those from motor vehicle fatalities, are suspect because depression or other emotional factors are frequently involved in car crashes. The investigating authorities, however, have cited all three as accidents and we have been unable to obtain any further details. The death of acquired immune deficiency syndrome was caused by an infection transmitted from a transfusion during a plastic surgery procedure at another hospital; the unknown death appears to have been a result of an arrhythmia.

Perioperative complications are listed in Table 6. Wound problems and infections are the most common cause of prolonged hospitalization in the severely obese, probably related to the high incidence of NIDDM. Table 7 lists those late complications that occur at a rate of 1% or greater. The most common problems seen over the 11 years of follow-up include depression and other psychiatric problems; vitamin and iron deficiencies; incisional hernias; cholecystitis; and technical problems associated with the operation such as staple line failures, anastomotic dilatations or stenoses, and bowel obstructions due to adhesions.

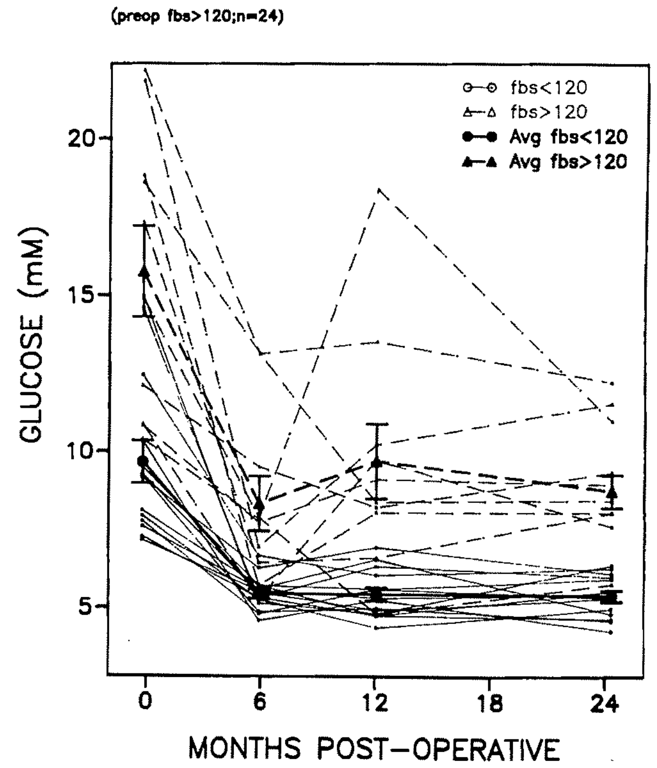

FIG. 3. Comparison between the postoperative fasting blood glucose levels in patients with NIDDM and preoperative plasma glucose readings of <120 mg/dL and >120 mg/dL. Patients with the higher preoperative glucose values experienced greater decreases in plasma glucose than their more normal counterparts, but leveled out at values that were still not fully normal.

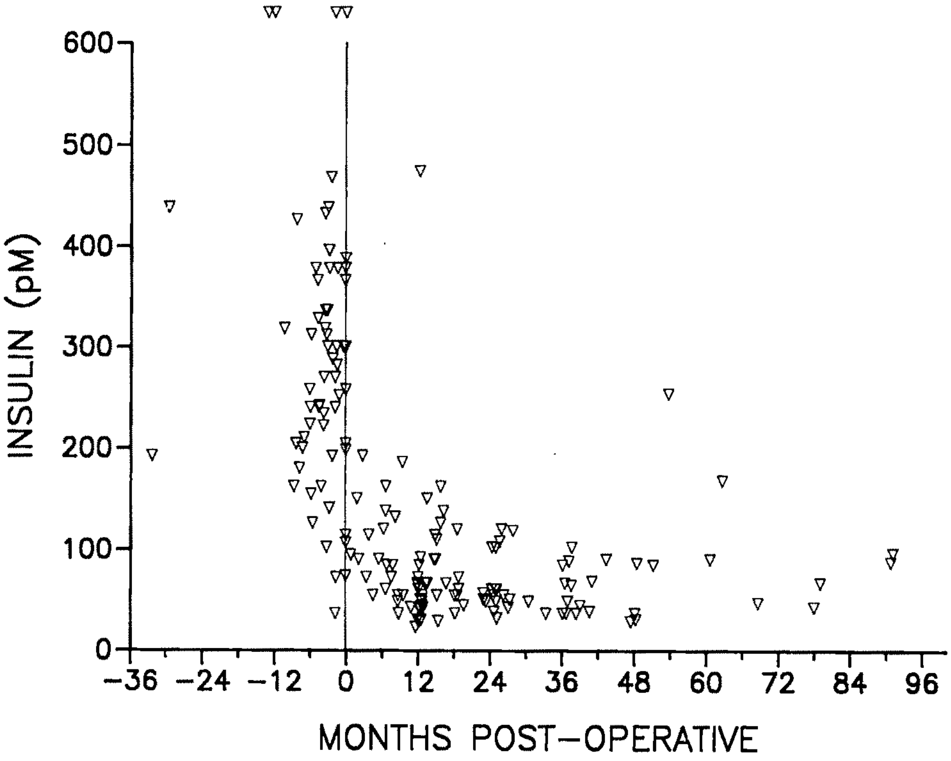

FIG. 4. Drop in insulin levels after the gastric bypass.

Discussion

One of the main goals in the management of NIDDM is euglycemia through weight control. Unfortunately, most patients with NIDDM are overweight, and further, NIDDM is especially common in patients who are severely obese, in other words, who exceed their ideal body weight by 100 pounds or more. Diets do not work in these massive individuals, and the general course of their illness is a pattern of ever-increasing weight, worsening diabetes, and progression of diabetic complications. Our data suggest that surgical intervention with the gastric bypass offers

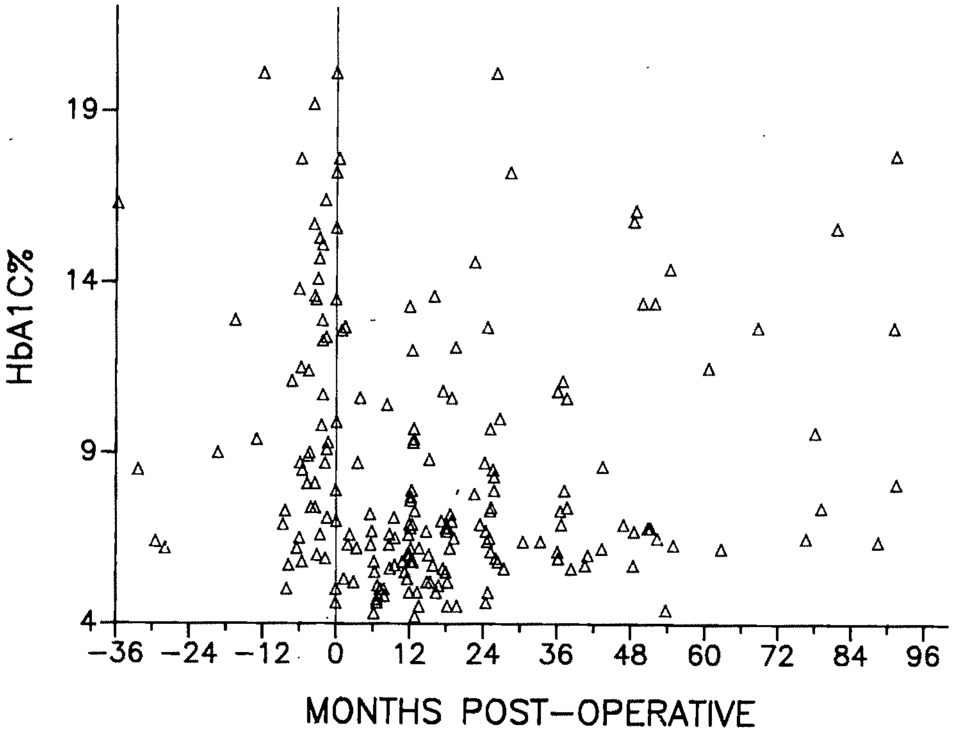

FIG. 5. Changes in Hb1Ac after gastric bypass. There is considerably greater scatter than is seen in the insulin levels.

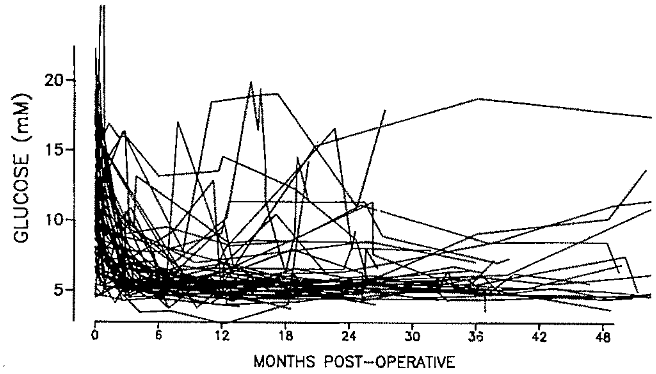

FIG. 6. Changes in fasting blood glucose levels after the gastric bypass. A great number of patients have reverted to normal values.

a new and reasonable approach to the control of NIDDM in the severely obese and perhaps in those who are moderately obese as well.

On March 25 through 27, 1991, the National Institutes of Health held a Consensus Conference on Gastrointestinal Surgery for Severe Obesity to examine the effectiveness of bariatric surgery. First, the panel concurred that severe obesity is an increasingly common problem: "The disorder is accompanied by reduced life expectancy and significant psychosocial and economic problems are frequently experienced by severely obese people." There is a direct relationship between the amount of excess weight and the incidence of arthritis, coronary artery disease, cerebrovascular disease, congestive heart failure, hypertension, diabetes mellitus, cholecystitis, and cancers of the stomach, uterus, and breast.[14,15] In addition, as they continue to get older and gain ever more weight, these individuals develop other health problems associated with severe obesity, including hypertension, cardiopulmonary failure, Pickwickian syndrome, sleep apnea, hyperlipidemia, coronary artery disease, gout, certain cancers, cholelithiasis, hepatic steatosis, polycystic ovary syndrome, pseudotumor cerebri, osteoarthritis, cardiomyopathy, hormonal abnormalities, and skin disease.

Patients, however, usually seek surgical intervention because of limitations in function rather than for health indications.[16] Fat people are frequently objects of public scorn and malicious ridicule. Employers are often reluctant to hire them because they are considered unattractive, have high rates of absenteeism due to illness, fall asleep on the job, and are thought to have a higher accident rate in factories because of their clumsiness and loose clothing. Obesity limits the availability of educational opportunities and a chance to find a spouse. Finally, our patients frequently mention their inabilities to meet their parental and other social roles: their children and other family members are ashamed to be seen with them at school, at athletic events, and in social situations. In short, the environment of the severely obese is neither happy nor filled with opportunities. Kral et al.[17] summarized their problems well when they concluded that the severely obese are handicapped by every measure: physically, emotionally, economically, and socially. Morbid obesity is indeed a serious disease; if diabetes is present as well, it becomes even more dangerous.

The estimated annual mortality rate in sudden death among the severely obese is 65/100,000, in other words, 40 times higher than expected in the general population.[11] An American Cancer Society study[18] disclosed deaths from all causes to be 50% higher among men and women who were merely 30% to 40% above normal weight. Mortality rate accelerates steeply when an individual becomes 50% overweight; for example, young severely obese males

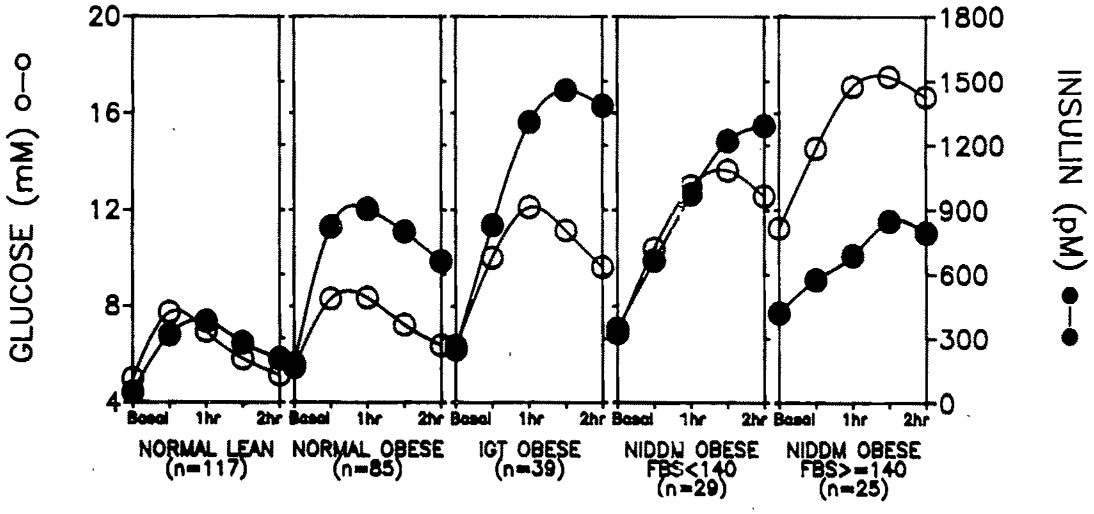

FIG. 7. Insulin resistance in normal and obese patients with and without diabetes as reflected by the oral glucose tolerance curves in 117 normal lean patients, 85 normal obese patients, 39 obese patients with IGT, 29 obese patients with NIDDM with FBS < 140 mg/dL, and 25 obese patients with NIDDM with FBS > 140 mg/dL.

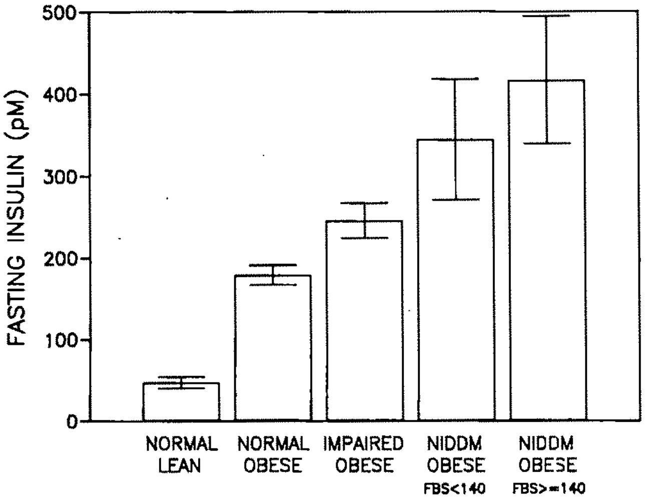

FIG. 8. Insulin resistance as reflected by the rise in fasting insulin levels in normal lean patients, normal obese patients, impaired obese patients, and diabetic patients with FBS < 140 mg/dL and > 140 mg/dL.

have a 12-fold increase in mortality rate.[19] Bray's[20] data, shown in Figure 9, graphically demonstrate the relationship of mortality to the body mass index (kg/m^2).

Second, the National Institutes of Health panel agreed that surgery has become the therapy of choice. According to the summary of the conference, more than 12 million Americans are severely overweight, and 4 million of these are "so overweight that their obesity harms their health and well-being, making them candidates for surgical treatment."[21] The panel endorsed two surgical treatments for severe obesity: vertical banded gastroplasty and the Roux-en-Y gastric bypass operation. These two procedures, gradually improved over the last three decades, can now safely and effectively control weight over long periods and either reverse or avoid many of the health and social problems associated with severe obesity. These operations are, however, not the only bariatric operations that ameliorate or reverse diabetes. Most operations reported to induce weight loss, including the intestinal bypasses, gastric bypasses, and gastroplasties, have shown this effect. It is our impression that the gastric bypass, with its bypass of the hormonal axis of the foregut and greater weight loss, does this more effectively than the gastroplasties, but our evidence for this remains fragmentary.

TABLE 5. *Deaths With Greenville Gastric Bypass After 11 Years' Follow-up*

Cause	N
Perioperative	
Sepsis	5
Pulmonary embolus	1
	6/515 (1.2%)
Late	
Suicide	3
Auto accident	3
Cirrhosis	2
Cancer	
Liver	1
Larynx	1
Myocardial infarction	1
Anemia, pernicious	1
Non-GGB sepsis	1
Malnutrition	1
AIDS	1
Unknown	1
Positional asphyxia	1
	17/515 (3.3%)
Total deaths	23/515 (4.5%)

GGB, Greenville gastric bypass.

TABLE 6. *Perioperative Complications With Greenville Gastric Bypass After 11 Years' Follow-up (N = 515)*

Complication Label	N
Wound complications	
Minor wound infection	50 (9.7%)
Wound seroma	35 (6.8%)
Severe wound infection	18 (3.5%)
Wound dehiscence	5 (1.0%)
Operative complications	
Spleen tear or laceration	13 (2.5%)
Subphrenic abscess	12 (2.3%)
Liver tear	8 (1.6%)
General complications after operation	
Temperature	45 (8.7%)
Anastomosis/stenosis	10 (1.9%)
Arrythmia	8 (1.6%)
Readmit	41 (8.0%)
Reoperate	12 (2.3%)
Patients with ≥1 perioperative complications	315 (61.2%)

Conclusion

The gastric bypass operation is an effective therapy for the treatment of NIDDM in the severely obese. The operation can be done with acceptable morbidity and mortality rates, and the effects of the procedure are well maintained over 11 years of observation. The procedure, with the modification that divides rather than staples the stomach, should now be considered for obese patients who are

TABLE 7. *Late Complications With Greenville Gastric Bypass After 11 Years' Follow-up (N = 507)*

Complication Label	N
Vitamin deficiency	233 (46.0%)
Anemia	232 (45.8%)
Readmit	187 (39.6%)
Depression	121 (23.9%)
Incisional hernia	107 (21.1%)
Gastritis	65 (12.8%)
Cholelithiasis	60 (11.8%)
Staple line failure	49 (9.7%)
Small bowel obstruction	28 (5.5%)
Dehydration/malnutrition	28 (5.5%)
Anastomosis failure	26 (5.1%)
Revision	25 (4.9%)
Ulcer	23 (4.5%)
Dilated pouch	17 (3.4%)
Anastomosis stenosis	15 (3.0%)

* Eight patients < 30 days after surgery.

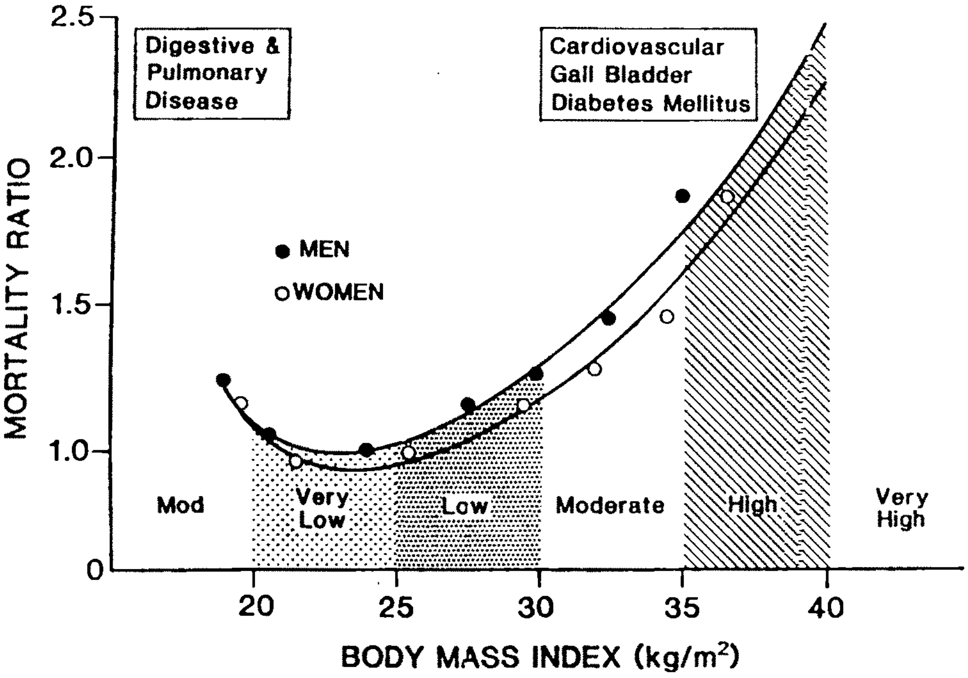

FIG. 9. Mortality rate rises sharply from all causes with increases in the BMI (kg/m^2). For reference, a woman 5'5" tall, with an ideal body weight of 134 lb. according to the 1983 Height and Weight Standards of the Metropolitan Life Insurance Company Tables has a BMI of 22.3. With a BMI of 30, 35, or 40, she would weigh 179 lb, 210 lb, or 240 lb, respectively. Patients are considered "clinically severely obese" or "morbidly obese" if they exceed a BMI of 35 with comorbid conditions or a BMI of 40 without obesity-associated illnesses. Reproduced with permission from Bray.[20]

not heavy enough to be classified as severely obese, but whose diabetes is difficult to control. Whether the euglycemia and restoration of normal insulin levels prevents the long-term development of diabetic complications remains unknown.

Acknowledgment

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DISCUSSION

DR. ROBERT E. BERRY (Roanoke, Virginia): Dr. Britt, Dr. Jones, Members and Guests, Dr. Pories and his group are to be complimented on their large series representing extensive experience in bariatric surgery. I was given the privilege of reviewing the manuscript and recommend it to you. Their patients appear well controlled. Their criteria for surgery are rigid, and they employ a meticulous operative procedure. I was privileged to watch Dr. Pories and one of his chiefs perform one of these procedures a few years ago. They have excellent close follow-up and, as he mentioned, representing 97% percent of the patients in the series. Dr. Pories' premise that the gastric bypass can control type II non-insulin-dependent diabetes mellitus in the obese patient is indeed a novel therapeutic approach. Whether surgery is the best approach for the obese patient may require a study, perhaps randomized and prospective. The authors also speculate whether the not severely obese patient may be a candidate for gastric bypass surgery to control diabetes in the future. Perhaps they will address this.

Several questions seem pertinent to this splendid study. Did you detect a postoperative change in endocrine function other than in the pancreas? You did do thyroid-stimulating hormone studies in your patients, as described in the manuscript. And, also, did the pancreatic exocrine function change? Of the 138 studied patients who maintained a normal fasting blood glucose level after operation, did you test the patients with a glucose tolerance test to determine an abnormal or normal result, which perhaps might be indicative of a long-term response? The study noted that wound problems were the most common perioperative complication, which you thought was probably due to the diabetes. Other studies suggest that diabetes mellitus is not always a factor in complications. Are the poor circulation and healing qualities of adipose tissue perhaps more important? Twenty-four of your patients received insulin before operation and yet were classified as non-insulin-dependent diabetes mellitus patients. Is the classification too rigid? Should the criteria be modified? That is, why is a type II non-insulin-dependent diabetes mellitus patient in that group when they do receive insulin? And, finally, does the type of operative procedure influence the outcome of the diabetes? Can the gastric banding procedure, perhaps, have the same result? I would like to thank Dr. Pories for allowing me to review the manuscript and the Association for the privilege of the floor. Thank you.

DR. R. SCOTT JONES (Charlottesville, Virginia): Thank you, Dr. Britt. First, I want to compliment Dr. Pories. This is obviously a carefully done clinical investigation, a large number of patients, 510 patients, and excellent results from the standpoint of a difficult surgical operation and surgical care. And I think that Dr. Pories and his team should be complimented.

I had a couple of questions that I wanted to ask about this material. First of all, in terms of the complications and not being able to ascribe alteration of complications to the operation, it is really not clear in my mind how well established the complications of this type of diabetes are. In other words, when we think — at least, when I think — about complications of diabetes, I am talking about a type I diabetic, and we talk about cataracts and vascular disease and renal failure and neuropathy, and so forth. What is the frequency of those complications in a population of type II diabetics compared with, for example, juvenile type I diabetics or adult onset type I diabetics?

And then the other question I had probably will be difficult to answer. Basically, we ascribe the metabolic abnormalities in these patients to the obesity; in other words, the hyperglycemia we ascribe to metabolic sequelae of the obesity. When we do the operation, a gastric bypass, we end up with several variables, which include weight loss, decreased caloric intake, and morphologic alterations of the upper gastrointestinal tract, which result in alterations in the way the organism assimilates and distributes nutrients. And I do not know whether it is really relevant or even important, but I would be curious to know your reflections on how you would sort these things out in terms of the metabolic effects. And I guess one way of looking at that, one way to sort out some of these things, would be to observe carbohydrate metabolism or insulin or what have you, over time, because, obviously, early after the operation they have not lost weight. And I was just wondering if you had done longitudinal studies that would provide insights into that kind of question. In any event, this is really excellent work, and I want to congratulate you and your group. It is really a monumental effort to do this work and follow patients carefully like you have, and we certainly appreciate your doing the work and sharing the information with us. Thank you very much.

DR. WALTER J. PORIES (Closing discussion): Let me thank my discussants for their gracious comments and thank all of you for staying.

The question was, how about a randomized study? We tried to do a randomized study but, unfortunately, when patients are morbidly obese and finally seek surgery, they are at the very end of the line. They are difficult to enter into a nonoperative group; when we managed to do so, they simply got their surgery done elsewhere. We have therefore been unable to mount a randomized study of surgery *versus* nonoperative care.

We are, however, conducting a randomized study of the gastric bypass, comparing it with a vertical banded gastroplasty to answer some of the questions that Dr. Jones posed. We have been unable to detect any changes in thyroid-stimulating hormone. The secretin or glucagon, and GIP studies are still frozen until we get a large enough group. We have done glucose tolerance tests on only a few of these patients because they will not tolerate an oral glucose tolerance test because they dump so badly. And after you try them once, they simply will not do that again. These patients have to be studied with intravenous glucose tolerance tests to define them.

I think your comments about wound problems are absolutely correct. Just the mass of fat must play a major role in having wound infections. How much diabetes affects the closure of wounds, I cannot tell you.

The classification of non-insulin-dependent diabetes mellitus, which is the question you raised, plagues us as well.

As you know, a type I or juvenile onset is called insulin-dependent diabetes mellitus, and type II or adult onset is called non-insulin-dependent, in spite of the fact that a significant number of these patients are on insulin. There are 1.2 million Americans on insulin who have NIDDM. Well, I think it is a bad term, and I wonder, frankly, whether the entire question of classification of diabetes should not be re-examined and whether we should not look at a preislet, an islet, a postislet, as well as a receptor, and then a postreceptor group. I think we would begin to think differently about the phenomena of diabetes. It has been observed that diabetes gets better with a vertical banded gastroplasty that does not bypass the antrum and duodenum. To what degree has never been well described, and this is why we are conducting our studies. And I cannot tell you, and I hope perhaps at a future meeting I will be able to tell you what the difference is in the diabetic response between the two because it forms an elegant experiment.

We also have done a number of studies in terms of peripheral nerve conduction, retinopathy, glucose clamp studies, and renal function. And, again, we will be able to report these, it is hoped, at another meeting.

The final question that is posed by Scott Jones is what about the complications? The complications in type 2 diabetes mellitus, which afflicts probably 92 percent of the 10 million people who have diabetes in the United States ends up being just as severe as the ones with type 1. It may be that the ones with type 1 develop somewhat faster in 20 years, but if you look at the diabetics who have type 2 diabetes, they account for most of our cases of amputation, of renal failure, and, indeed, of blindness. Again, I thank all of you for your patience and for the courtesy of letting me give this paper.

The Surgical Management of Infants and Children With Ambiguous Genitalia

Lessons Learned From 25 Years

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Over a 25-year period, 91 children with ambiguous genitalia have received surgical management. Female sex assignment was made for 79. Of these, 60 patients underwent extensive clitoral reconstruction consonant with the female assignment. Forty-two patients had vaginal reconstruction. Factors relating to success include: (1) prompt and appropriate sex assignment; (2) early and accurate diagnosis; (3) conservative reconstruction of the clitoris at an early age (less than 1 year); and (4) choice of vaginal reconstruction based on the severity of the malformation. Long-term follow-up demonstrates satisfactory anatomic and functional results when clitoral surgery alone was required. Functional results for patients with extensive vaginal reconstruction have been compromised. Physicians caring for children with congenital intersexual anomalies can expect to encounter a wide spectrum of anatomic and physiologic derangements. Cosmetic appearance alone is an inadequate measure of success because endocrinologic, social, psychological, and sexual factors must be blended into comprehensive evaluation of these patients. The management plan must be flexible and individualized, incorporating long-term follow-up to adulthood.

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AMBIGUOUS GENITALIA, WHICH herald some variant of intersexual malformation, are now recognized immediately in the newborn nursery. The tragedies of yesteryear when an adolescent girl would suddenly grow facial hair or a teenaged boy would develop breasts unexpectedly rarely occur. Diagnostic tools are available for use in the first days of life, which permit assessment of biochemical derangements, determination of genotypic pattern, and definition of internal genital anatomy. Based on these observations, an accurate and appropriate sex assignment can be issued with confidence and dispatch. This decisive step is urgent, minimizing the psychosocial impact of a parent rendering an equivocal or evasive answer to the age-old question from loved ones, as to the sex of the new baby. Once the sex of rearing is firmly established, a plan for the required surgical correction and its timing assumes paramount importance.

From the patients reported here, certain principles have been derived that have been found helpful in managing these complex clinical problems over the last 25 years.

Materials and Methods

Ninety-one children with ambiguous genitalia have been cared for since 1966 at our institution. The follow-up ranges from 1 to 24 years, with a mean of 8 years. The clinical records of all patients were analyzed. Additionally, many patients have been seen regularly, others sporadically, and, sadly, some have been lost to follow-up. The results of the last examination were reviewed, and when available the older patients were brought back for full evaluation. Outcome was evaluated as to appearance, and of special importance, older patients were subjected to assessment of psychosocial and sexual function. A single surgeon provided the unified, continuous surgical care of these children. The comprehensive support that these patients need was provided by nurses, neonatologists, pediatricians, endocrinologists, psychologists, and parents.

Diagnosis and Sex Assignment

In the newborn infant, a precise diagnosis is achieved by combining the results of the physical examination with the laboratory evaluation. The location of the gonads, the adequacy of the phallus, the size and location of a vaginal orifice, if present, are assessed (Fig. 1). A rectal examination provides information concerning the presence of a uterus or prostate gland. Introduction of x-ray contrast

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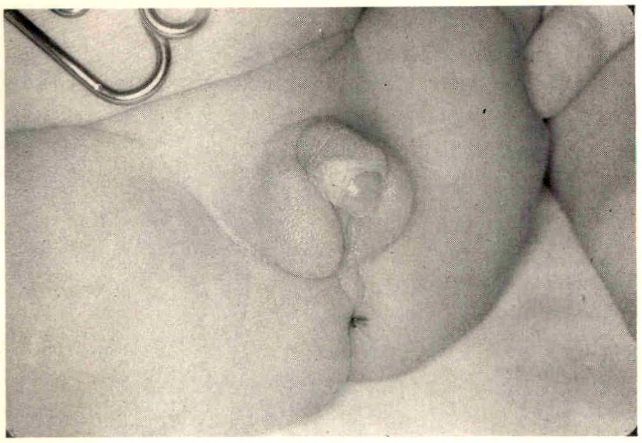

FIG. 1. Ambiguous genitalia as seen in the newborn.

into a urogenital sinus outlines the internal urethral and vaginal anatomy (Fig. 2). Ultrasonography supplies useful information concerning the internal pelvic organs.

An expeditious laboratory evaluation is carried out to determine the specific genotype and pathophysiologic cause for each child. The chromosomal makeup is determined from the presence of chromatin on a buccal smear and blood cell karyotype analysis. Serum electrolytes, steroid levels, and urine metabolites pinpoint errors in steroid biosynthesis. Although many sophisticated tests are becoming available, the absolute initial requirement is a rapid determination of the genotype, and identification of the potentially life-threatening salt-losing adrenogenital syndrome.

When all information from the physical examination, the laboratory, the radiologic/imaging studies, and, in rare instances, exploratory laparotomy is at hand, the sex of rearing can be assigned with confidence. The male role is naturally elected for all genotypical males born with hypospadias and undescended testicles. Male pseudohermaphrodites, including some with testicular feminizing syndrome, an occasional true hermaphrodite, and some infants with gonadal dysgenesis may be successfully reared as males, if, and only if, they are born with a male-sized penis. A small subgroup of male (XY genotype) patients exists who are born with hypoplasia of the penis. These patients suffer from interruption of the synthesis of dihydrotestosterone (5-alpha reductase deficiency) or other poorly understood causes of phallic inadequacy. Because the phallus is so small as to resemble a clitoris, these patients are unsuited for the masculine role and must be raised as girls.

All of the female patients with congenital adrenal hyperplasia as well as females with clitoromegaly from other causes should be reared as girls. These patients constitute approximately 90% of the entire cohort with intersexual malformations, and most require some form of reductive surgery for the clitoris. In addition, most will need vaginal reconstruction.

In practical terms, regardless of the genotype, most children with ambiguous genitalia are best suited for the female role. In the highly selected cases to be brought up as males, the crucial determinant is the size of the phallus, that is, whether it is adequate to support a male sex assignment. If not, female sex assignment is made and planning for total rehabilitation is outlined. This program of comprehensive staged surgical reconstruction, and in many patients, a lifetime of exogenous medication is thoroughly discussed and repeatedly explained to the parents. Such discussion must be regularly revisited.

Male Reconstruction

Fewer than 10% of patients born with the intersex anomalies will be directed to a male sex assignment. These male patients are culled from the group of male pseudohermaphrodites, or occasionally a child with mixed gonadal dysgenesis, or more rarely a true hermaphrodite. The surgical requirement for male sex of rearing is the

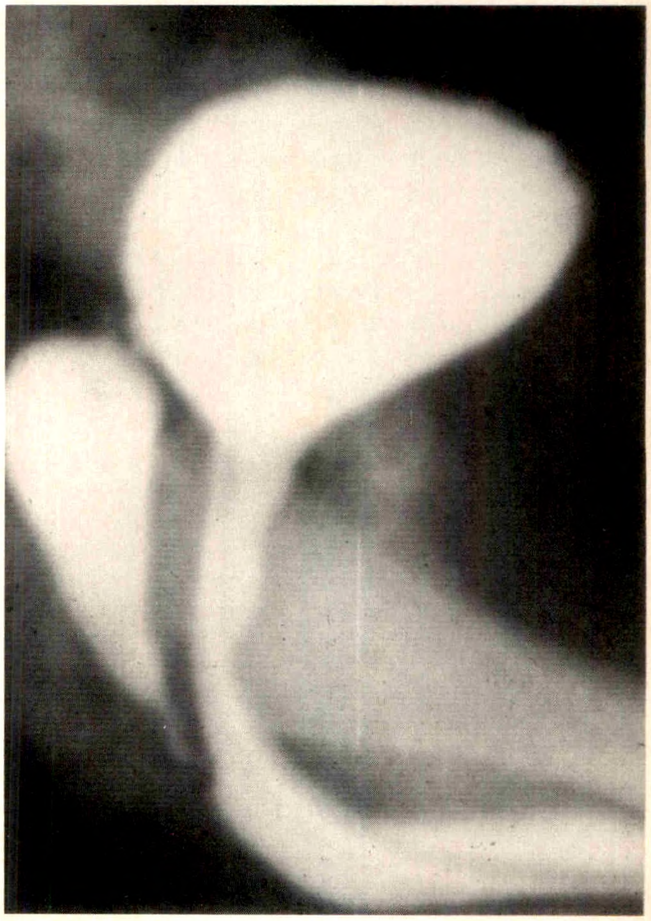

FIG. 2. X-ray study with contrast filling the urethra and bladder, showing distal vaginal atresia and urethrovaginal fistula (type C).

presence of a sufficiently large phallus to function as a male urinary conduit, to offer a satisfactory appearance when compared with peers, and to function satisfactorily for sexual activity (Fig. 3).

Of those patients most appropriate for a male sex assignment, the least complicated are those with XY genotype who happen to be born with one or both testes undescended, and have an associated hypospadias. Physical examination of such newborn infants discloses a confusing external genital presentation, which requires the standard workup. It is sometimes necessary to perform an exploratory laparotomy to obtain gonadal tissue for confirmatory histology and to exclude Müllerian remnants. Such patients engender the least social stigmata and can be set on their life path as whole and healthy males with two standard operations: orchidopexy and hypospadias repair.

In those more complex patients to be raised as male, notably a rare true hermaphrodite, or more commonly those pseudohermaphrodites with a normal-sized penis, several orderly steps lead to reconstruction. If Müllerian duct structures persist in the pelvis, they are surgically removed. These structures may include an ovotestis, Fallopian tube, uterus, and proximal vagina; the distal vagina should not be dissected for fear of injuring the adjacent nerves. This maneuver leaves a persistent diverticulum on the posterior urethral wall, but is to be favored over the possibility of causing impotence.

External genital reconstruction requires repair of hypospadias. Deformities of labial tissue must be rearranged to eliminate feminine folds around the penis, and to fashion a satisfactory scrotal pouch (Fig. 4). In those patients with an undescended testicle that is otherwise normal, orchidopexy is indicated. For children with gonadal dysgenesis, imperfect or streak gonads must be removed to avoid malignant degeneration. Testicular prostheses are recommended as the youngsters reach adolescence.

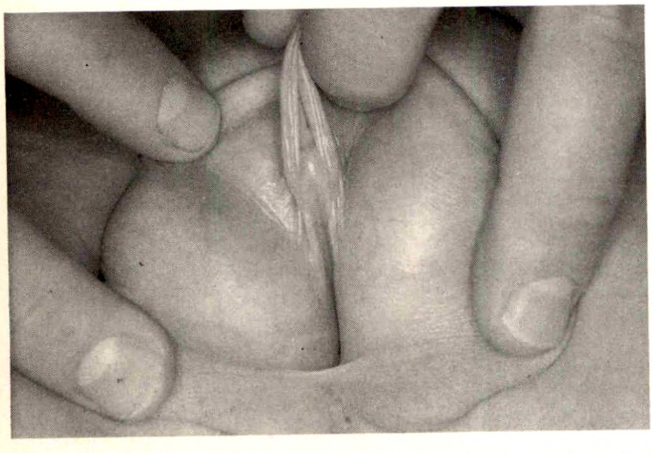
FIG. 3. Genotypic male with end organ defect. This inadequate phallus determines female sex of rearing. Phallus length is compared with published "normal" values.[41]

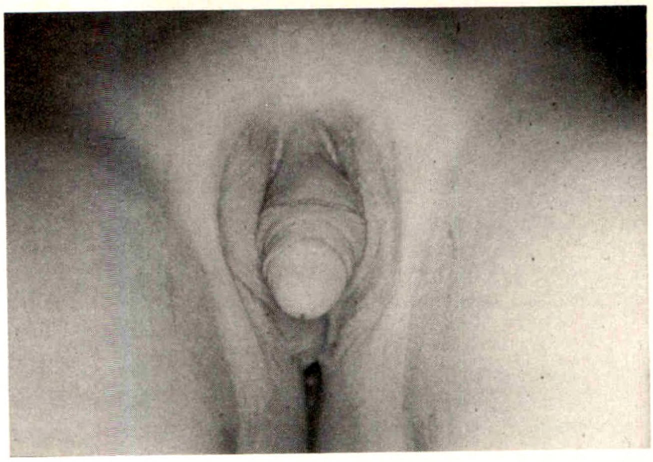
FIG. 4. Male pseudohermaphrodite with penis adequate for male sex rearing. Transposition of labia to create scrotum to maximize masculine appearance is essential.

Female Reconstruction

Clitoral Reconstruction

Most patients with intersexual malformations are best suited for female sex assignment. These infants have been derived from a wide range of diagnoses, and most require surgical correction of an enlarged clitoris (Table 1). It is the clitoral-sparing recession operation, devised in our institution, which we have used in the series of patients reported here.[1] The basic tenets of the operation, described in detail in previous reports, are seen in Figure 5. These are: (1) removal of the excess skin over the enlarged clitoris; (2) dissection of the shaft with preservation of the neurovascular bundle; (3) division of the suspensory ligament; (4) protection of the underlying urethra; (5) seating the clitoris in a retrograde manner beneath the pubis; and

TABLE 1. *Diagnoses of Patients With Ambiguous Genitalia at Children's Hospital, Washington, DC, 1966–1991*

Diagnosis	No.
Congenital adrenal hyperplasia	46
Maternal ingestion of hormones	9
True hermaphrodite	4
Male pseudohermaphrodite	7
Idiopathic	5
Gonadal dysgenesis	4
Congenital absence of the penis	2
Simple XY hypospadias with undescended testicles	6
Cloacal anomalies	6
Vaginal atresia	1
Mosaic XO–XY	1
Total	91

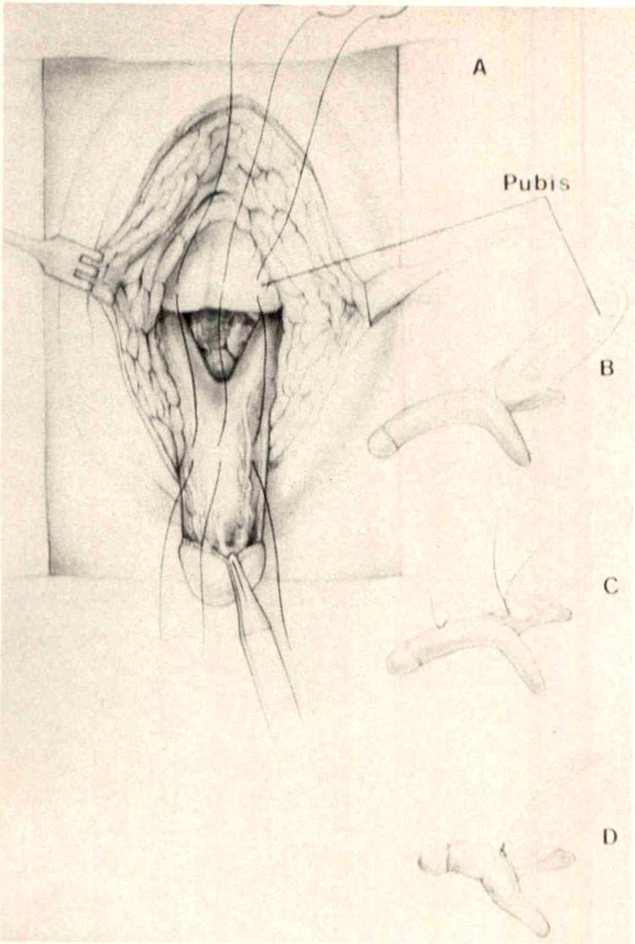

FIG. 5. Basic diagram of elements of clitoral-sparing recession. Note preservation of the corpora with recession to the undersurface of the pubis.

(6) anchoring the clitoris in the new position with sutures taken in Buck's investing fascia, which are then affixed to the periosteum of the undersurface of the pubis. The surrounding fatty tissue is then brought together in the midline to recreate the mons veneris, which further minimizes the visible part of the clitoris (Fig. 6). For some patients in whom the circumference of the glans is so large as to be disfiguring, we have developed a reduction glansplasty. The anterior wedge excision results in a more delicate feminine glans clitoris (Fig. 7).

Vaginal Reconstruction

In these patients, four basic operations have been used, depending on the degree of vaginal malformation. Cystoscopy and contrast studies are useful adjuncts to define the anatomy. We currently categorize the vaginal anomalies as follows:

Type A. Simple labial fusion
Type B. Distal urogenital sinus formation
Type C. Distal vaginal atresia with proximal urethrovaginal fistula
Type D. Complete absence of the vagina

Each of these deformities requires a different reconstructive approach. The complexity of the surgery increases with the severity of the vaginal malformation.

For type A (simple labial fusion), a midline division of the labia shows a normal hymeneal ring and a normal or near-normal urethral meatus. After division of the labia, the skin and mucosal layers are approximated to assure that the introitus remains open, creating a normal appearance.

For type B (distal urogenital sinus formation), a more extensive separation of the fused tissue is required. It is necessary to develop a posterior pedicle flap from the labioscrotal tissue, which then is sutured to the vagina, creating a satisfactory opening for the urinary and genital orifices.

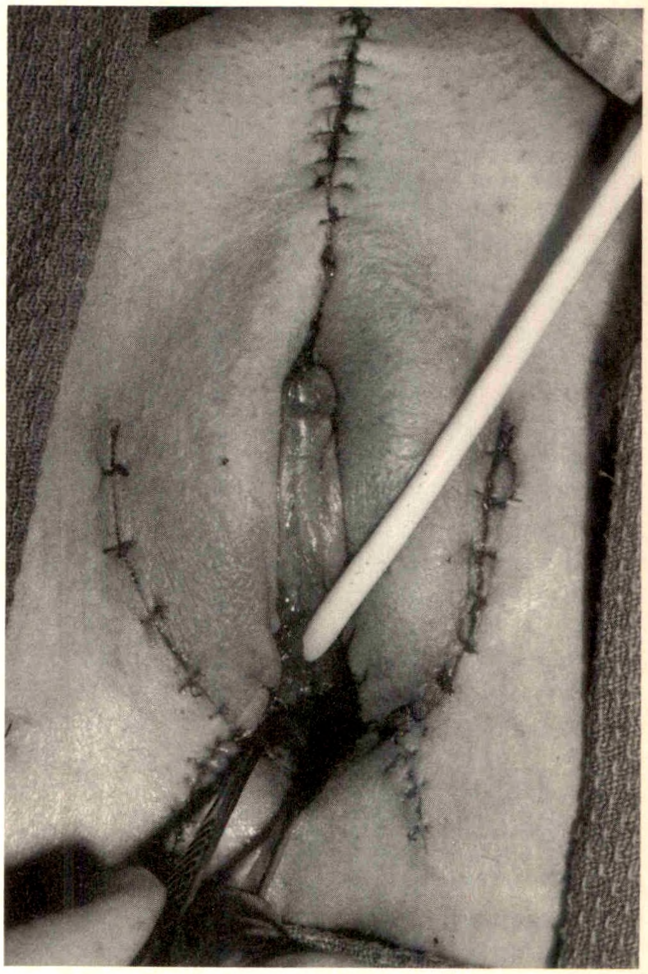

FIG. 6. Appearance immediately after surgery, showing recession clitoroplasty and vaginal reconstruction. Note reconstruction of introitus using labioscrotal folds.

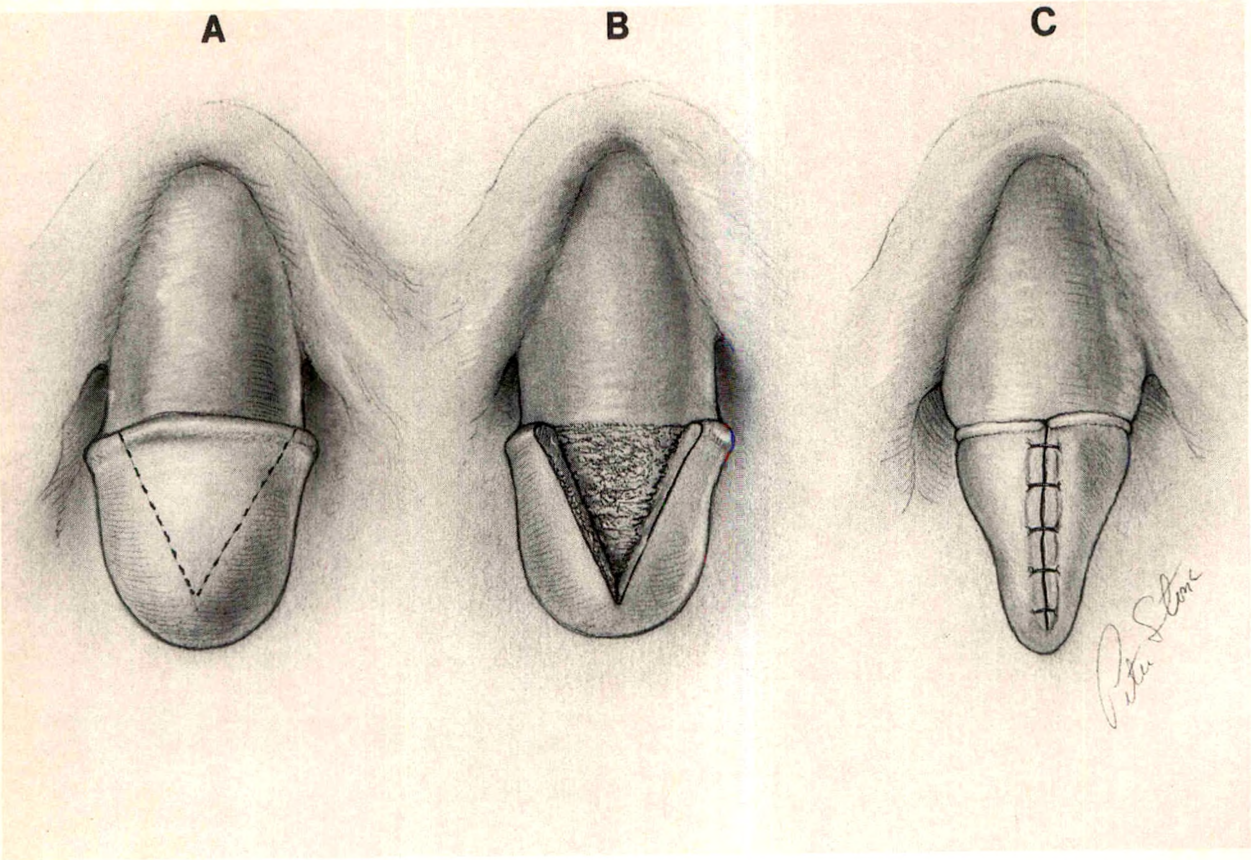

FIG. 7. Operative diagram showing glansplasty for children requiring reduction in circumference of glans to enhance feminine appearance.

In those patients with type C anomaly (distal vaginal atresia with proximal urethrovaginal fistula), we have performed a vaginal pullthrough operation using a perineal approach. With the patient in the lithotomy position, a series of flaps are outlined and elevated. The dissection is carried into the soft tissue beneath the urethra. Hendren and Crawford have recommended the insertion of a Fogarty catheter into the vagina through the urethra and the urethrovaginal fistula.[2] With the Fogarty balloon partially expanded, recognition of the vagina is simplified. The vagina is separated from the urethra, and the urethral defect is closed over a catheter. The pedicle flaps of labioscrotal tissue are then sewn to the vagina to separate it from the urethra and to permit exteriorization of the vagina.

In some patients, the circumference of the vagina at its junction with the external pedicle flaps will become inadequate or frankly stenotic. In such circumstances, we have resorted to the use of large well-vascularized pedicle flaps derived from the inner aspect of the thigh. These flaps are outlined just below the skin crease between the leg and the groin. The narrow vagina is incised longitudinally from outside, well inward to the midvagina. The elevated flap is drawn into the defect and sutured, thus widening the circumference of the vagina. When additional width is required, bilateral flaps are used.

Patients requiring complete vaginal replacement (type D) have thus far been encountered only rarely. As we have followed our patients into adolescence and now adulthood, however, it is becoming apparent that more patients will require total vaginal reconstruction. We have used a number of different methods to reconstruct the vagina, including chronic dilation, perineal flaps, pedicle flaps from the inner thigh, and molded stent skin grafts. None of these methods has proven fully satisfactory, and therefore we have recently embarked on a program of vaginal reconstruction/replacement using a sleeve of transplanted colon. The blood supply of the colon permits it to be mobilized and easily transposed into the pelvis. Perineal dissection allows the colovaginal transplant to be brought into the proper position anterior to the rectum and sutured to the surrounding labioscrotal tissue, which has been fashioned into an introitus (Fig. 8).

Results

Ninety-one patients were evaluated with ambiguous genitalia. In the first decade, approximately 30% were not

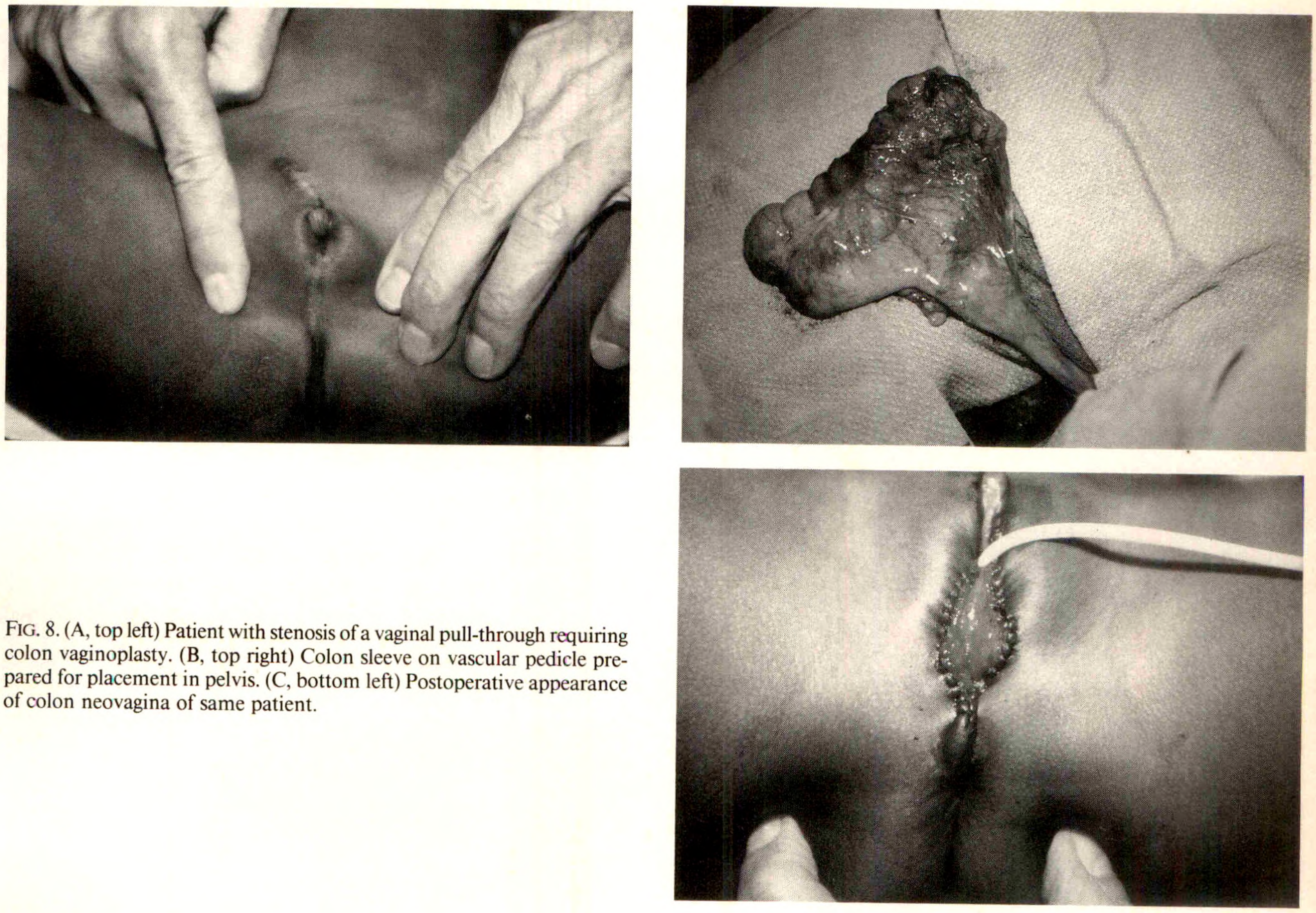

FIG. 8. (A, top left) Patient with stenosis of a vaginal pull-through requiring colon vaginoplasty. (B, top right) Colon sleeve on vascular pedicle prepared for placement in pelvis. (C, bottom left) Postoperative appearance of colon neovagina of same patient.

recognized as newborns. In the last decade, all patients were recognized in the newborn period. Of the 91 patients, 12 were managed as males. Seventy-nine received female sex assignment and were raised as females. Although most required surgical intervention, 10 females were followed without operative management.

Of the 79 female children, 60 had clitoral surgery. In the very early days of our experience, clitorectomy was the favored operation; since 1966, however, clitoral-sparing recession has been employed in most patients (Table 2). Forty-two children had vaginal surgery (Table 3).

Appearance

The external appearance of virtually all of the patients with female sexual assignment is judged as satisfactory at present (Figs. 9, 10). A significant number of children required secondary operations such as a second clitoroplasty (26%) or glansplasty (15%) to achieve satisfactory cosmetic appearance.

TABLE 2. *Operations for Clitoral Reconstruction*

Procedure	No.
Clitoral recession	53
Clitorectomy	7
Total	60
Revision	16
Second revision	2
Glansplasty	9

Function

At this time, appraisal of function is incomplete; however, 20 patients were available for long-term follow-up into adulthood. Twelve had clitoral surgery alone. Ten of these show highly satisfactory social, psychological, and sexual function. One patient demonstrates partial success but has pain with orgasm, and one has dyspareunia. Of

TABLE 3. *Vaginal Reconstruction*

Procedure	No.
Simple introitoplasty	
Incision and opening	10
Labial excision	2
Posterior flap	7
Pullthrough	14
Skin graft	3
Thigh pedicle	4
Colon	2
Total	42

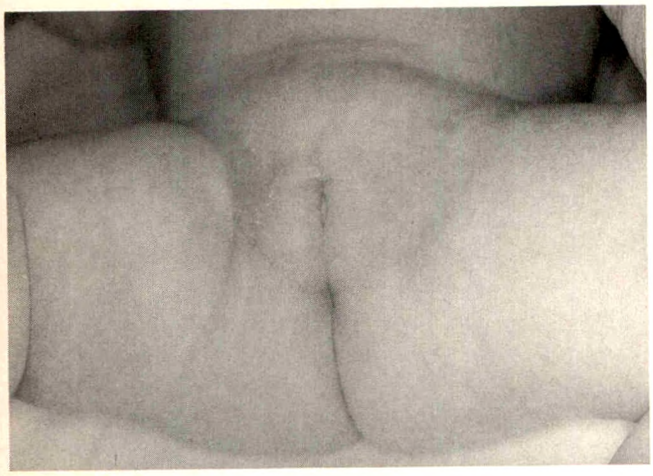

FIG. 9. Child 1 year after clitoral recession showing satisfactory feminine contour.

the remaining eight adult patients who underwent extensive vaginal as well as clitoral surgery, most have achieved acceptable results in social and psychological adjustments, but sexual function has ranged from satisfactory to poor. Two of the four patients with thigh flaps continue to have problems with vaginal size. Eight of the 14 with a vaginal pullthrough (type C) developed severe stenosis requiring secondary operations; additionally, three patients have been discovered with uncomfortable growth of hair at the introitus.

Discussion

The patients selected for the male role constitute slightly less than 10% of all infants born within the spectrum of diagnoses encompassing the intersex syndrome. As with all such patients, each requires precise and prolonged follow-up of their appearance, of their function, and for psychosexual adjustment. As part of a program of ongoing counseling, these young males must come to understand the abnormality, and when appropriate, the absence of sex glands, and the need for exogenous hormone support. Further, with some exceptions in the group of males born with the less complicated variant of hypospadias and undescended testicle or testicles, most of these children will be sterile. For all of our patients, males and females who will be sterile, it has been our practice to instruct the parents to eliminate from their conversation, and thus from their child's thinking, all traditional references to genetically transmitted characteristics, for example, "He has his mother's eyes," "He has a big nose like his father," or "He gets his stubborn streak (as an inherited trait) from his uncle John." Instead, because the future family constellation of sterile adults will probably include adopted children, the emphasis must be on the paramount importance of love between family members, and how that emotion is the key to family bonding.

With respect to males born with an end-organ defect resulting in penile hypoplasia, at the current state of knowledge, they must be raised as females. Experience has shown that the most heartbreaking maladjustment attends those patients who have been raised as males in the vain hope that the penis will grow to a more masculine appearance and size "at a later date." The phallus of such individuals is so small as to resemble a clitoris; thus, they are doomed to life as a male without a penis. We, as others, have concluded that, until such time as enzymatic synthesis can produce adequate and predictable growth of the penis in these infants, they must be raised as females. This assignment is made contradictory to the patient's XY genotype in the full awareness that exogenous hormone therapy and extensive surgery for vaginal replacement will be necessary. However, the required comprehensive rehabilitation program is preferable to a male life without a penis. Because the clitoral-like phallus is properly innervated, orgasm and sexual function in the female role is theoretically achievable, although none of the pa-

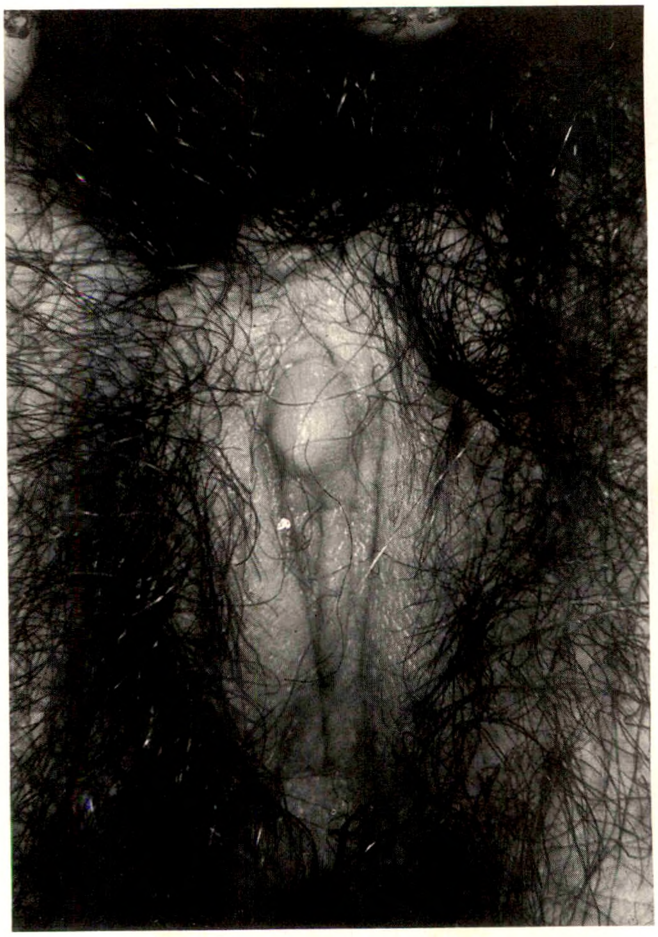

FIG. 10. Appearance of a 19-year-old patient whose clitoral recession was performed at 5 years of age. Note the accommodation of genital components.

tients available for study in this series have been followed into adult life.

Males born with congenital absence of the penis are extremely rare; two such patients have been encountered in this group over the 25-year study period (Fig. 11). Surgical rehabilitation is achieved by performing orchiectomy because, as in patients with penile hypoplasia, female rearing is the only reasonable course. A female distal urethra is constructed, positioning it appropriately in the introitus, which is fashioned from the skin of the normal scrotal pouch. Colovaginoplasty can be performed if the patient desires this, but ultimate adjustment is marginal at best, because all erotic tactile stimulation is congenitally lacking.

The existence of a normal-sized penis in patients assigned a male role is comforting to the parents even when hypospadias is present. Conversely, female babies born with an ungainly masculine enlargement of the clitoris evoke grave concern in their parents. Our experience suggests that once the female sex of rearing is made, the parents are usually calmed by a full explanation of the child's pathophysiology, and the promise of major corrective surgery within 3 to 6 months. This age has seemed ideal for the clitoral-sparing recession operation in our hands. The babies who require daily medication, as in the salt-losing adrenogenital syndrome, are stabilized by 3 months of age, and the infant's size at 3 months is more conducive to the requirements of the clitoral operation than that of a newborn infant.

There are two major approaches to plastic reduction of the enlarged clitoris, and each has strong support. Resection of all but the tip of the glans clitoris with preservation of the nerve and blood supply was suggested in early work by Goodwin,[3] and has been championed by others.[3–8] The cosmetic effect is excellent. Late studies with assessment of sexual gratification, orgasm, and general psychologic adjustment are unavailable for these patients and remain in question. Burying the enlarged clitoris by drawing surrounding fat over it was suggested by Lattimer in 1959.[9] This was the first effort to preserve all of the clitoris, as opposed to complete corporal resection.[10] In 1966 at our institution a procedure was developed that preserves all of the clitoris, and after full dissection, permits its recession beneath the central pubis with preservation of all nerves, blood supply, and corporal bodies, allowing erection without cosmetic offense.[1] Over the years, this operation has worked well, but has required a second procedure in a number of children, a third in several patients, and a glansplasty in others. Conservation of all of the clitoris, including its erectile function, would seem to provide the best chance for the patient to achieve normal orgasm in adult life. In fact, only the total clitoris-sparing recession operation has had any long-term assessment for sexual function in children who have grown to adulthood.[11–13] Results from these rather rudimentary studies are so encouraging as to make a strong case for retaining the entire clitoral organ.

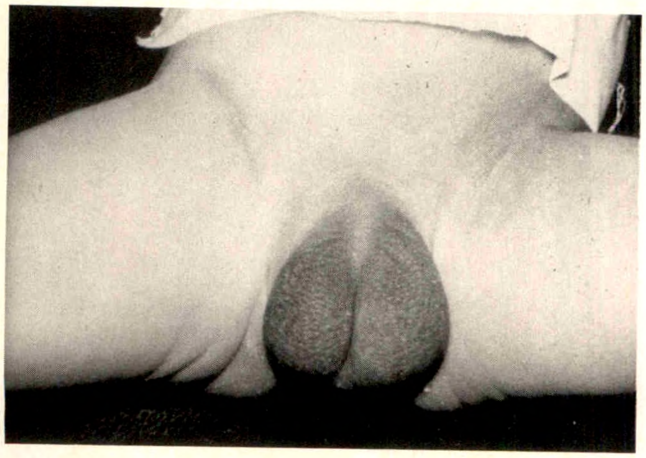

FIG. 11. Congenital absence of the penis in an infant requiring female sex assignment.

Construction of an introitus has brought forth a variety of plastic surgical tissue-moving maneuvers by surgeons working with these patients.[14–24] Some final results are more acceptable than others. In those patients (types A & B) requiring the simpler forms of introitoplasty, excellent feminine appearance and a satisfactory passage for sexual congress can be achieved. The delicate labia minora are difficult to simulate, however, even with the most creative surgical approaches, and the mucus-secreting glands of the normal introitus are congenitally absent in most of these patients.

The pullthrough vaginoplasty to reconstruct patients with distal vaginal atresia and urethrovaginal fistula (Type C) is an elaborate technical exercise involving extensive perineal dissection. The exteriorization of the vagina and, separately, of the urethra is immediately achieved, and the early appearance is satisfactory. Long-term follow-up of this operation, however, has disclosed a number of problems. The first difficulty, found in most of these children, is the unavoidable absence of the mucus apparatus of the normal introitus. The second is the frequent tendency toward stricture formation at the union of the proximal vagina and the external pedicle flaps. The third, and perhaps most objectionable feature is the development of a tangle of hair at the introitus emanating from the inturning flaps of scrotal-like skin. As our results indicate, many of these patients require secondary operations to improve function or appearance.

The complete absence of a vagina necessitates creative surgical reconstruction to simulate a vagina (type D). Although total replacement of the vagina using a sleeve of transposed colon has been used in only two patients in this group, it has proven highly satisfactory in early evaluation. The colon is favored over the small bowel because the stretch pain fibers of the smaller diameter small intestine might lead to dyspareunia. The mucus surface of the colon has salutary functional implications for the neovagina. Additionally this operation can be performed early in life; our younger patient was 3 years old at the time of colovaginal replacement.

With respect to evaluating and reporting results of this study, several variables are at play. First is the steady increase in knowledge about the subject matter.[25-27] Understanding of this spectrum of pathology and physiology has been evolving over the four decades since Lawson Wilkins' discovery of the deranged physiology in children born with congenital adrenal hyperplasia.[28] A second obstacle of even greater importance in the reporting of surgical results is the ongoing progress in operative approaches for correcting the deformities that these children present.[29-35] Further, it has become obvious to all workers in this field that sexual function and psychosocial adjustment are the main goals for these patients, rather than simple assessment of their genital appearance.[36-40] It is these subjective factors, so difficult to quantify, that are the ultimate determinants of successful surgical reconstruction.

In this regard, it is difficult to emphasize adequately the compelling need for an ongoing care program encompassing, physical, endocrinologic, and psychologic needs for each patient and each parent caught in the web of the intersex phenomenon. We have learned, in some instances bitterly, the absolute essentiality of a structured, regular, comprehensive program from infancy, through the turbulent adolescent years with its sexual awakenings, and, finally into adult life. This program must have decades-long continuity, and the team must include a pediatrician, an endocrinologist, a psychiatrist or psychologist, and a nurse as well as a surgeon experienced in the vexing surgical problems these fascinating young patients present.

Conclusions

1. Patients with any form of the intersexual malformations benefit from recognition on the first day of life.
2. A comprehensive battery of diagnostic tools is available to pinpoint the pathologic derangement, and to allow accurate sex assignment in a matter of hours, or at the most, days after birth.
3. An effective program of surgical rehabilitation can be undertaken in the early months of life.
4. A program spanning infancy to adulthood must be set up to provide all physical and psychologic needs for the patient and family.
5. Late maladjustment, sexual failure, and psychic distress can largely be avoided today by an informed health care team acting in concert over the patient's lifetime.

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DISCUSSION

DR. BIEMANN OTHERSEN (Charleston, South Carolina): Dr. Ochsner, Dr. Jones, Ladies and Gentlemen, I appreciate the opportunity to discuss this fine presentation and to have reviewed the manuscript. To amass this number of patients with ambiguous genitalia in itself is a real accomplishment. But what comes through in the manuscript is not just meticulous medical and surgical care of these children, but also real compassion and concern for them and their families. This is a stressful situation to every mother and father presented with a child with this problem. I would like to stress the admonition of the authors here about gender assignment and what problems occur when you make the wrong assignment quickly and without a lot of thought and study. As an example, children with exstrophy of the cloaca often have an intussusception of the terminal ileum through the exostrophied bowel, and it looks like a phallus. And you have to address that right away, because if these are boys and you try to raise them as a boy, as they brought out in the paper, it is impossible because of lack of a functional phallus or penis.

I would like to ask a question that may concern a situation that would present itself to any general surgeon who takes care of children with hernia—that is, that is a normal-appearing girl with a hernia and a gonad in the hernia sac. If you open the sac and find the gonad and there is no Fallopian tube, some would advise biopsy of the gonad to make sure this is not testicular feminization or male pseudohermaphroditism. Even though the child looks like a girl, the organ is a testis. If you see a normal Fallopian tube in addition to the gonad, does this mean that the gonad is an ovary or does it mean you should still perform a biopsy on that gonad? Thank you. I enjoyed this presentation very much.

DR. JUDSON RANDOLPH (Closing discussion): Well, Dr. Othersen has raised a good question. If the gonad in a girl's hernia is free of the Fallopian tube, we always biopsy. We take a good, hard look at the others. Sometimes they are odd-looking ovaries, and they might be ovo-testes, or they might even, in the male pseudohermaphrodite, be testes. If there is anything odd, we perform biopsies, but not on every one. Thank you very much for your discussion.

Nissen Fundoplication in Children With Profound Neurologic Disability

High Risks and Unmet Goals

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Anti-reflux procedures have been advocated in children with profound neurologic disability referred for feeding gastrostomy when gastroesophageal reflux is present. Facilitation of care, reduction in pneumonia and vomiting, and improvement in the general health and survival of these children have been major goals of fundoplication and gastrostomy. In large pediatric series, these procedures have been reported to have low risk and negligible mortality rates. Recent reports, however, document an increased incidence of sequelae of fundoplication in children with profound neurologic disability. This paper retrospectively reviews a series of 35 nonverbal, nonambulatory pediatric patients undergoing a total of 39 fundoplications (37 Nissen, 1 Thal, and 1 Belsey) over an 11-year period. Neurologic impairment of 17 (49%) patients was acquired, 13 (37%) congenital, and 5 (14%) due to a syndrome. Perioperative complications occurred in six (17%). Three additional complications led to early postoperative death. A fourth early death was unexplained. Fourteen (40%) had recurrent pneumonia, 11 (31%) recurrent vomiting, 8 (23%) choking-gagging-retching complex, and 3 (9%) bowel obstruction requiring laparotomy. Recurrent gastroesophageal reflux was documented in seven (20%) patients. A second ARP was performed in six (17%). There were 14 (40%) late deaths. Although the major goals of anti-reflux procedure are clearly achieved in many severely impaired children with gastroesophageal reflux, the use of Nissen fundoplication to resolve the complications of swallowing disorders and improve outcome with an acceptably low risk in this complex set of patients does not appear to be established.

RESOLUTION OR PREVENTION of complications of gastroesophageal reflux (GER) and facilitation of care with as few complications as possible are the primary goals of the anti-reflux procedure in a neurologically impaired child. These goals are achieved in most such patients.[1-3] Recent studies, however, have documented the significantly higher morbidity and mortality rates after fundoplication in neurologically impaired as compared with neurologically normal children.[4-7] For example, neurologically impaired children underwent reoperation in the late postoperative period four times as frequently and had over four times the combined failure rate (reoperation rate plus aspiration-induced deaths) as neurologically normal children in one large series from two institutions.[5] This report raises again the question whether the benefits of Nissen fundoplication in a particularly severely affected group of patients—those with profound neurologic disability—are worth the benefits.

Materials and Methods

From January 1, 1979 to December 31, 1989, 113 anti-reflux procedures were performed in 104 patients on the Pediatric Surgical Service of the Medical University of South Carolina. Thirty-nine of these procedures were performed in 35 patients classified as having profound neurologic disability; one additional patient was lost to long-term follow-up and was excluded from the study. The charts of these 35 patients were reviewed for demographic data, clinical symptoms, diagnostic tests, early and late morbidity and mortality rates, and resolution of preoperative symptoms.

All patients were nonverbal, nonambulatory, profoundly retarded, and incontinent. Younger patients were considered to have poor prognosis for ambulation or improvement in cognitive skills. There were 18 males and 17 females, ranging from 3 weeks to 22 years of age (mean, 4 years 6 months). Initial operation at our institution occurred in 26 patients in the last 3 years of the study period. Mean follow-up was 30 months. Acquired neurologic impairment was present in 17, congenital neurologic impairment in 13, and syndrome with neurologic impair-

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ment in 5 (Table 1). Eight had tracheostomy, eight ventriculoperitoneal shunt, and at least 11 were blind. Incidence of conditions that tend to raise intra-abdominal pressure and possibly contribute to the development and recurrence of gastroesophageal reflux[8] are listed in Table 2. Another cause of acutely raising intragastric pressure and thus contributing to fundoplication failure—overfeeding through gastrostomy—was not documented in our patients, but may well have occurred. The incidence of delayed gastric emptying in this series cannot be estimated because only two gastric emptying tests were performed. Primary and secondary indications for fundoplication appear in Table 3. The prophylactic category was defined as fundoplication performed in a patient referred for feeding gastrostomy, who had no history of aspiration pneumonia, for whom vomiting was not a major problem, and in whom preoperative diagnostic testing showed at most mild reflux. There were no esophageal strictures in this series.

Thirty-seven upper gastrointestinal series were performed in 26 patients; six patients had esophageal pH study and one each a milk technetium scan, a gastric emptying study, and esophagoscopy. Quantitative assessment of the severity of gastroesophageal reflux in these patients was not possible in this retrospective review because of lack of uniformity in the number and technique of the tests employed. For example, systematic grading of the severity of gastroesophageal reflux on barium swallow was not routinely assessed, nor was there a standardized protocol for performing these studies in these patients, many of whom had barium placed in the stomach by tube because of inability or refusal to swallow. Nine patients underwent fundoplication solely on the basis of clinical symptoms. Follow-up in 22 of 31 patients alive 1 month after fundoplication consisted of 37 gastrointestinal series, three esophageal pH studies, and again a single milk technetium scan, gastric emptying study, and esophagoscopy. Mention of failed medical management was found in only eight patients and consisted of various combinations of positioning, cimetidine, metoclopramide, and antacids. It was assumed that an attempt at medical management had been made by referring physicians, but specific documentation of this treatment was lacking.

TABLE 1. *Cause of Profound Neurologic Disability*

Cause	No. of Patients
Acquired neurologic impairment	
Perinatal asphyxia	6
Complications of prematurity	6
Child abuse	2
Left hemispherectomy for intractable seizures	1
Transposition of great vessels with anoxia	1
Closed head injury	1
Congenital neurologic impairment	
Cause undetermined	8
Congenital cytomegalovirus	1
Microcephaly	1
Congenital hydrocephalus	1
Degenerative neuromuscular disease	1
Cerebral hemiatrophy	1
Syndrome	
Trisomy 18	1
Down's syndrome with perinatal asphyxia	1
Wernig–Hoffman	1
Undefined	1

TABLE 2. *Conditions Raising Intra-abdominal Pressure in 35 Patients*

	No. of Patients
Seizure disorder	23
Spasticity	18
Pulmonary disease	17
Chronic constipation	8
Choking–gagging–retching	8
Scoliosis	5

There were 33 primary procedures (33 Nissens, 1 Thal) and six reoperations (5 Nissens, 1 Belsey, the only transthoracic procedure). Two reoperations were performed on patients undergoing primary Nissen fundoplication at other institutions. Two patients had gastrostomy before fundoplication. At the time of anti-reflux procedure, all patients had gastrostomy and one had pyloroplasty. Gastrostomy was requested in many instances because trials of nasogastric feeding were poorly tolerated because of either patient discomfort or caretaker inconvenience. It was assumed that the addition of fundoplication at the time of gastrostomy would be associated with very low additional morbidity or mortality rates and would—by preventing complications of gastroesophageal reflux present before operation or developing after gastrostomy placement—be expected to be of substantial benefit to these patients. For these reasons, no attempt was made during the period of this study to randomize patients into groups receiving gastrostomy alone and gastrostomy with fundoplication.

Results

There were nine major complications within the first month of fundoplication. Three led to death and three

TABLE 3. *Indications for Fundoplication*

Indication	Primary	Secondary
Aspiration pneumonia	13	6
Vomiting	11	9
Prophylactic	10	0
Failure to thrive	2	28
Hematemesis	1	2
Gastric outlet obstruction	1	0
Apnea	0	3
Paraesophageal hernia/pain with feeding	1	0
Stricture	0	0

required reoperation (Table 4). Hepatic vein laceration occurred in two reoperations; in one, exsanguinating hemorrhage led to death from multiple organ failure. Bilateral tension pneumothorax developed after tracheostomy performed at the time of fundoplication in one patient. A second infant with bronchopulmonary dysplasia had pneumothorax that developed after emergency intubation and resuscitation in the recovery room. Gastric outlet obstruction was due to a rapidly performed, technically unsatisfactory anterior fundoplication in another infant who had severe unexplained rigidity during operation. Successful conversion to Nissen fundoplication was performed 4 days later. Jejunal perforation found on reoperation 2 days after fundoplication was believed to be secondary to chronic steroid administration for pituitary insufficiency in an infant with cerebral hemiatrophy and "empty sella" syndrome; death was caused by resultant gram-negative sepsis. Fluid and electrolyte imbalance led to the death of a 2.5-kg 7-month-old child. Death possibly due to aspiration occurred unexpectedly at home 2 days after uneventful hospitalization for fundoplication in a 5-week old baby.

Nine patients, two of whom had a primary Nissen procedure at other institutions, developed paraesophageal hernia, seven with recurrent GER. Five of these patients underwent reoperation for recurrent GER. One patient, the only one in the series with history of esophageal atresia, has recurrent GER after a second fundoplication. Two patients required laparotomy for small bowel obstruction. Fourteen patients died more than 1 month after fundoplication, nine within 15 months of operation. Hospital deaths were due to associated disease. Home and institutional deaths were poorly documented, but complications of fundoplication or recurrent symptoms of GER were not mentioned as causative factors.

Incidence of postoperative pneumonia, vomiting, and choking-gagging-retching is shown in Table 5. Five patients with recurrent pneumonia showed marked improvement on discontinuation of the anticonvulsant clonazepam, which can cause increased salivation.[9] Five patients with relatively mild episodes of pulmonary infection responded to medical therapy; pneumonia did not recur in two after reoperation; and two had ongoing respiratory problems despite negative workup for recurrent GER. Postoperative vomiting resolved in three patients undergoing reoperation; of the remaining four with recurrent vomiting, only one persists with this symptom. Two patients with postoperative choking-gagging-retching have had complete resolution, whereas for the remaining six this has been of mild severity. Of the 30 patients with preoperative failure-to-thrive, 14 showed improvement in growth and three required caloric restriction due to excessive weight gain. Fourteen remained on the same growth curve, and two fell below preoperative levels. Hematemesis resolved in three. Patients with apnea continued to have apneic episodes, but died of other causes. The child whose primary indication for fundoplication revision was paraesophageal hernia in association with apparent pain with feedings died of complications of intraoperative hepatic vein laceration.

TABLE 4. *Early Morbidity and Mortality*

	No. of Patients
Complication	
Hepatic vein laceration	2
Bilateral tension pneumothorax	2
Jejunal perforation	1
Small bowel obstruction	1
Gastric outlet obstruction	1
Acute renal failure	1
Sacral decubitus	1
Deaths	
Multiple organ failure	1
Gram-negative sepsis	1
Acute renal failure	1
Suspected aspiration	1

TABLE 5. *Symptoms (n = 35)*

Symptom	Before Surgery	After Surgery
Pneumonia	22 (63%)	14 (40%)
Vomiting	28 (80%)	7 (20%)
Choke–gag–retch	4 (11%)	8 (23%)

In the 10 patients undergoing "prophylactic" Nissen, there were two early deaths due to surgical complications and six delayed deaths due to associated disease. Two patients with occasional episodes of pneumonia, but no documented preoperative GER, had continuing respiratory problems that resolved in one when clonazepam was discontinued and in the other, who also had recurrent vomiting and paraesophageal hernia, with reoperation. Intermittent preoperative vomiting in six others resolved. Choking-gagging-retching in another remained unchanged after fundoplication.

In nine patients who developed paraesophageal hernia, 7 had seizures, 5 spasticity, 4 pulmonary problems, 2 scoliosis, and 1 each constipation, delayed gastric emptying, and choking-gagging-retching. Seven patients had at least two of these problems, and four had three or more. Two attending surgeons performed or supervised performance of all fundoplications. Because of the widely varying ages and sizes of the patients and varying degrees or completeness in operative summaries, it was difficult to draw any meaningful conclusions about differences in technique between failed and successful fundoplications; however, it was noted that in 5 of 7 primary Nissens performed at our institution and later developing paraesophageal hernia, the crura were repaired with nonabsorbable sutures without pledgets. When reoperation was performed in two of the patients who had initial operation elsewhere, no evidence of pledgets was found in the vicinity of the crura.

Discussion

Most patients in this study benefitted from fundoplication and gastrostomy. Enteral access had been established and most symptoms of GER resolved or had been medically managed by the time of death (in the 14 patients whose death was apparently not related to fundoplication). Of the 17 survivors, two of whom have undergone a second fundoplication, none currently have persistent vomiting or pneumonia. Our bias, however, that fundoplication in these patients should carry minimal associated morbidity and mortality rates, was not borne out by our results. All four early deaths occurred either as a direct result of a surgical complication (hepatic vein laceration) or indirectly as a result of the stress of a major surgical procedure (jejunal perforation, acute renal failure, and suspected aspiration). None of the late deaths could definitely be attributed to complications of fundoplication, but in many cases the cause of death either at home or at a chronic care facility was poorly documented. For example, one 22-year-old patient was reported to have died 5 months after operation at a chronic care facility of a "heart attack," yet an entry in the chart at the time of death described the patient's abdomen as being distended. Without a postmortem examination, the possibility of death due to aspiration complicating yet another bowel obstruction can not be ruled out. The fact that nine of the late deaths occurred within 15 months of fundoplication suggests that this procedure was of limited benefit to these individuals. Furthermore, reoperation was common in relatively short follow-up: three laparotomies for bowel obstruction and six reoperations for failed fundoplication. Although preoperative symptoms in most of the 17 survivors are satisfactorily controlled, 14 patients (40%) have had recurrent pneumonia; 11 (31%), recurrent vomiting; and 8 (23%), choking-gagging-retching complex. Three additional patients have been documented as having a paraesophageal hernia, but have not undergone reoperation.

Since our retrospective review has documented increased morbidity and mortality rates in profoundly neurologically disabled pediatric patients, our threshold for preforming a fundoplication in a neurologically impaired child referred for a feeding gastrostomy has been raised. We believe it is critical to demonstrate before operation that GER is the cause of symptomatology and that risks involved in submitting them to this major surgical procedure are worth the benefits. Preoperative evaluation ideally should separate those whose aspiration and vomiting is due to GER rather than nasopharyngeal incoordination, esophageal dysmotility, primary "antral dysmotility,"[10] or medication, as in our patients whose recurrent pulmonary infections resolved only after clonazepam was discontinued. The reliability, feasibility, and cost-effectiveness of various diagnostic tests are controversial, but, as a minimum, a contrast study and an esophageal pH study or endoscopy with biopsy seem reasonable both before operation and in long-term follow-up when symptoms recur.[11] "Protective" anti-reflux operation has been advocated in all neurologically impaired children undergoing feeding gastrostomy, even in the absence of GER, because of the incidence of GER developing *de novo* after Stamm gastrostomy and percutaneous endoscopic gastrostomy.[12] This recommendation has been challenged recently on the grounds that only a minority of mentally retarded children without GER require anti-reflux procedures after gastrostomy.[7,13] In those who do require fundoplication subsequently, staging the two procedures does not seem to expose these patients to excessive morbidity rates and may, in fact, reduce risks as a result of improved nutrition from gastrostomy feedings.[14] In addition, right-sided "gastrostomy with anti-reflux properties" placed in the lesser gastric curvature has been advocated on the basis of results in a small series of neurologically impaired children without GER[15] and in a cat model.[16] Our experience in our small group of "prophylactic" Nissens emphasizes the potential risks of a policy of "protective" anti-reflux operation.

When fundoplication is indicated for symptomatic GER, it is not clear that a Nissen is the best choice. The incidence of wrap breakdown/paraesophageal hernia and small bowel obstruction after Nissen fundoplication in this group of children is disturbingly high.[5,17] Some of these failures may be due to lack of adherence to certain technical details of the procedure, as emphasized by DeMeester et al.,[18] Johnson,[19] and Pearl et al.[5]: short, floppy wrap performed over a large bougie; deep, nonstrangulating crural stitches reinforced with pledgets; suture fixation of the esophagus to the crus (as in the Thal repair); and securing the wrap to the undersurface of the diaphragm with interrupted nonabsorbable sutures. Further modifications of the Nissen technique may reduce wrap herniation into the chest.[20] Addition of pyloroplasty in patients demonstrated to have delayed gastric emptying may explain the lower incidence of wrap breakdown in Fonkalsrud et al.'s series.[21] A partial gastric fundoplication has both theoretical and actual advantages. By allowing retrograde release of excessive intragastric pressure (due to seizures, scoliosis, delayed gastric emptying, distal migration of gastrostomy balloon,[22] etc.), partial fundoplication may be less prone to wrap breakdown. Thal fundoplication has been reported to have a much lower incidence of subsequent hiatal hernia and small bowel obstruction.[23]

In summary, the results of Nissen fundoplication in our series of patients with profound neurologic disability confirms the experience of others who report increased risks of death, recurrence of symptoms, paraesophageal hernia, and small bowel obstruction in these children as compared with neurologically normal patients. Further refinements in diagnostic and treatment strategies are needed to improve patient selection and reduce risks in this markedly impaired group of children.

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DISCUSSION

DR. HOWARD FILSTON (Knoxville, Tennessee): President Ochsner, Secretary Jones. C. D., that was a beautiful presentation, and I appreciate and am privileged to discuss your paper. Dr. Smith and his associates have quite courageously taken a critical look at their results in anti-reflux operations for profoundly neurologically damaged infants and children and, thereby, have documented what all of us who care for these unfortunate children have come to realize: By our usual standards, these patients have an inordinate number of complications and are very significant mortality risks after these procedures. Without surgical intervention, however, these patients have been difficult to feed, have failed to thrive, and have been plagued by retching, aspiration, recurrent pneumonia, and a high mortality rate. The current report has the usual limitations of a retrospective review lacking matched controls. One has only historical impression for comparison.To evaluate critically the significance of the 40% late mortality rate would require an age and severity matched study, with patients randomized to nonoperative treatment, partial fundic wrap, and full Nissen fundoplication, preferably done by a limited number of surgeons using a standardized technique. This is a big order for a pediatric surgery service that accrues 35 such patients in more than 10 years.

Furthermore, to recognize technical difficulties and complications unique to or excessive after anti-reflux procedures in the neurologically damaged group would require an analysis of these same factors in their 69 patients who were not considered severely damaged. Perhaps Dr. Smith could comment on the incidence of complications and failures in this other group. Despite these limitations, there are some valuable lessons to be gained from this report. First, these neurologically dysfunctional children have multiple sphincter, motility, and secretion abnormalities. Therefore, it is mandatory that each be thoroughly evaluated for swallowing abnormalities, excessive secretions, esophageal dysmotility, delayed gastric emptying, and constipation in addition to a full anatomic and physiologic study of their gastroesophageal-sphincter mechanisms to select those patients whose gastroesophageal reflux is a significant enough part of their dysfunctional problems that they would benefit from operative correction.

Two, related abnormalities such as delayed gastric emptying must be simultaneously corrected. Given the rate of complications, including recurrent reflux and hiatal hernias, prophylactic fundoplication concomitant with feeding gastrostomy cannot be advocated unless gastroesophageal reflux is clearly documented.

Third, there are technical details of the fundoplication, the value of which needs to be better demonstrated, especially in these patients with their propensity to herniation and breakdown.

And, finally, the determinant of value and success for anti-reflux procedures in these profoundly damaged patients may need to focus more on factors other than deaths and complications. These include decreased number and duration of hospital stays, more dependable feeding routines, and reduced vomiting and aspiration, making it easier for the overburdened parents to find secondary care givers. Dr. Smith's report shows that most of these patients do benefit from these procedures, so that perhaps improved patient selection will help to limit their application to those that can be expected to benefit. Thank you.

DR. JUDSON RANDOLPH (Washington, DC): Mr. President, excuse me for rising again, but I had the opportunity to read this paper, and it is courageous, honest, and calls to mind the fact that we do not have full answers for this complicated group.

May I show one slide, please? I thought it worth showing this alternative approach. In those patients with very poor esophageal function, if one adds an antireflux wrap at the GE junction, the problem is increased rather than diminished. As suggested first by Putnam of Rochester, a jejunal Roux-en-Y loop attached to the disassociated esophagus permits the feeding to proceed with the certainty that there is no reflux. And secretions and a bit of nourishment can be taken to augment the gastrostomy feedings. Finally, if there should be improvement in the neurologic condition, this arrangement is reversible. The third point I wanted to make in just a moment is the terrible ethical dilemma surgeons face with these patients. This courageous report gives us an idea of how much help we are rendering them, and we must ask ourselves if we are increasing the ease of their care. We know that the parents love them and have great affection for them, but we are setting up a situation where these patients with serious neurologic impairment are going to outlive their parents, and I do not know that that is a kindness. I think we have to evaluate this thorny element as well as the physiologic problems, and I hope Dr. Smith would comment on this area of concern.

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): Dr. Ochsner, Dr. Jones, Ladies and Gentlemen. I rise also to comment on Dr. Smith's courage in presenting this, as has also been noted — to bring before a group of surgeons a paper that clearly says "stop operating" or look very carefully at what you are doing. But this is also Dr. Smith's very first paper before this august organization, and I think that takes courage also. And, as always, it is difficult to extend Dr. Randolph's comments. I think also the anguish we all feel needs to be emphasized because those of you who do not care for these children may not realize how frequently we are asked to make this decision. In our own unit in Baltimore, we are seeing more than 50 such patients and operating on them each year.

Now these patients do not come off the street; they are referred by our pediatric neurologists, and so they are being evaluated by another echelon of care. So there are a large number of physicians and care givers who are also anguishing over this decision. The real question is: Are we becoming a part of the patient's disease? And in so doing, are we not supporting the families but prolonging their agony? That is the focus that we must all have as we try to decide which patients should receive surgery.

A couple of objective comments: Many of these children have swallowing difficulties rather than gastroesophageal reflux. C.D., how do you separate that group? They are not going to be helped by an anti-reflux procedure. As a matter of fact, they may have more difficulty in swallowing. We are now looking at a prospective double-blind study in which we are doing only gastrostomies in this group of patients and no anti-reflux procedures, hoping that we can convince the parents that at least we have done something to help this group of children and that perhaps they will go along with that for the short period that many of these severely neurologically damaged children have ahead for them.

This is the third commonest operative procedure we are asked to do in our pediatric surgery service. After hernia repair and central venous access, this constitutes the largest number of operations. That is a tremendous burden and a major problem. For these reasons, I think this is not only a courageous paper but a very wise one.

DR. C. D. SMITH (Closing discussion): Thank you very much for those comments from three people I admire a great deal. Dr. Filston mentioned that this was a retrospective review, and it would be nice to have a prospective review. I think that is the major thing to come out of this for us. Our data show that this operation has many complications in the severely neurologically impaired child. We should present these risks to the family and not just recommend this procedure as an automatic knee-jerk type thing. I think it is clear that there are a number of options and they need to be evaluated prospectively. I would hope that several pediatric surgical centers can get together to evaluate in prospective fashion all patients like this who present for consideration for a fundoplication as well as a feeding gastrostomy.

Dr. Randolph mentioned the Putnam procedure. Perhaps it could be evaluated as part of such a prospective study.

The ethical dilemma is a major one. My approach to these patients has certainly changed. Rather than saying, "Well, the child needs a feeding gastrostomy, let's add a fundoplication," I say "Let's look at the whole patient. What is the outlook? What are the things that are really bothering you? These are the things that I can do." I think the parents are the ones who need to make the decision as to what treatment—including the surgical treatment—should be done.

Dr. Haller asked a question about how we separate out the ones who are having swallowing problems from the ones who have problems related to gastroesophageal reflux. I think it is clear we did not study these patients enough. We clearly need to study these patients more extensively and decide which ones actually need or could be helped by fundoplication and which ones actually might be worse as a result of a fundoplication. The upper gastrointestinal series is one essential series. A pH study is another. We do not have the capability to do manometrics, but this can be helpful in sorting out those patients whose primary problem is a delayed gastric emptying and not really gastroesophageal reflux at all. This is a point that has been emphasized by Rick Fonkelsrud in Los Angeles.

Finally, I would like to thank the Association for the privilege of membership — it has meant a great deal to me — and for your patience in listening to material with which many of you have much more experience than I.

Laparoscopic Appendectomy

Initial Experience in a Teaching Program

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From February 1990 to December 1991, 16 laparoscopic procedures were performed for right lower quadrant pain. There were nine men and seven women, aged 16 to 47 years (mean, 27.2 years). All procedures were performed by surgical chief residents with prior experience in laparoscopic cholecystectomy, first-assisted by an attending surgeon. The appendix was visualized and a definitive diagnosis was made in all patients. One patient with acute salpingitis underwent diagnostic laparoscopy only; two patients underwent laparotomy (perforated appendicitis, perforated diverticulitis). A fourth patient had an acute torsion of an ovarian cyst managed laparoscopically. Laparoscopic appendectomy was successfully performed in 12 patients (acute appendicitis, 9; fibrosis or chronic inflammation, 2; normal appendix, 1). Mean operative time for laparoscopic appendectomy was 95.7 minutes, and mean postoperative stay was 2.5 days. The authors conclude that operative time, diagnostic accuracy, and complication rates for laparoscopic appendectomy are acceptable. Within the context of a training program, laparoscopic appendectomy provides an opportunity for surgical residents to expand laparoscopic skills.

OPERATIVE LAPAROSCOPY WAS introduced into the teaching program of the University of Mississippi Medical Center in February 1990. A 2-day didactic program composed of the basics of laparoscopy, equipment trouble-shooting, and safety considerations followed by laboratory experience in a porcine model preceded clinical exposure for all residents. Diagnostic laparoscopy for right lower quadrant pain preceded the first laparoscopic cholecystectomy, and the first laparoscopic appendectomy was performed several months later. From the beginning, surgical residents were active participants, performing over 95% of procedures with an attending surgeon as first assistant. This report details the experience with the first 16 laparoscopies performed for right lower quadrant pain, including 12 laparoscopic appendectomies, and includes all such cases treated by three attending surgeons (CSC, TJH, FFM) from February 1, 1990 through November 30, 1991 (22 months). It summarizes our total institutional experience to date.

Methods and Materials

All patients admitted to the gastrointestinal surgery service at the University of Mississippi Medical Center during the study period with right lower quadrant pain were considered for laparoscopic appendectomy (LA). Initially, the procedure was reserved for patients with right lower quadrant pain and equivocal signs and symptoms of appendicitis who had failed a trial of observation. Patients with clear signs of appendicitis were treated by open appendectomy. With experience, these latter patients were managed laparoscopically as well. Patients with generalized peritonitis, significant abdominal distension, or dilated loops of bowel on x-ray were managed by open appendectomy. Pregnancy was considered an absolute contraindication for LA, as was a history of a bleeding diathesis. The nature of the procedure and possible complications were explained to the patients before operation, and consent was obtained for laparoscopic as well as for open appendectomy.

All patients at University of Mississippi Medical Center who undergo laparoscopic procedures, including LA, are entered into a computerized surgical laparoscopic registry. Demographic information, preoperative signs and symptoms, white blood count, temperature, x-ray findings, length of procedure, nature of procedure performed, whether or not conversion to open surgery was required,

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surgeon, first assistant, location of appendix (retrocecal *versus* intra-abdominal), pathology, postoperative stay, complications, and follow-up are recorded. In addition, the number of open appendectomies performed on the service during this same time period was recorded.

Surgical Technique for Laparoscopic Appendectomy

The patient was positioned supine, with both arms tucked at the sides. An indwelling urinary catheter and nasogastric tube were placed to decompress the bladder and stomach. The surgeon (chief resident) and camera driver (junior resident or medical student) stood at the patient's left side, the first assistant (attending surgeon) stood to the right. The video monitor was placed at the right side of the table, below the first assistant (Fig. 1).

Laparoscopy was performed by a closed technique. If the findings were consistent with acute appendicitis, or if no other cause was found for the pain, the patient was placed in steep Trendelenberg position. A second trocar (5 mm) was placed in the right lower quadrant, lateral to the rectus sheath (Fig. 2), under direct vision. The first assistant placed an atraumatic or bowel-grasping forceps through this trocar and gently displaced the omentum and cecum with a sweeping motion. Sometimes the appendix became visible at this point; more commonly, it was not.

The third trocar (11 or 12 mm) was placed in the midline and suprapubic. If the patient was small, this trocar was placed to the left of the midline to allow sufficient working distance between trocars and avoid "crossing swords" within the confines of the abdominal cavity (again, the rectus muscle was avoided). This trocar will hereafter be termed the "working trocar," because it is through this port that the surgeon operates. The surgeon placed an atraumatic grasping forceps through the working trocar and grasped the appendix if it was visible. If the appendix was not yet visible, the surgeon grasped the cecum and retracted it cephalad.

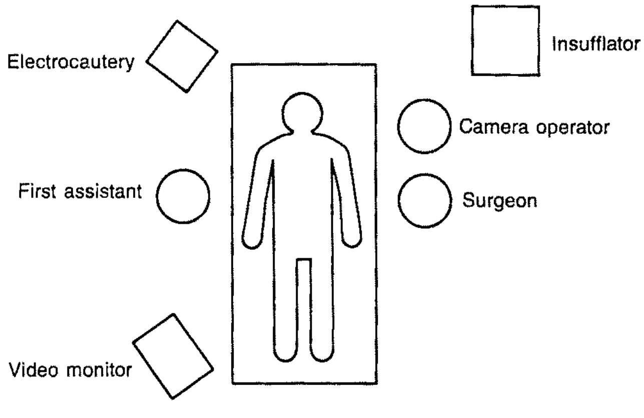

FIG. 1. Position of surgeon, first assistant, camera driver, insufflator, electrocautery, and video equipment.

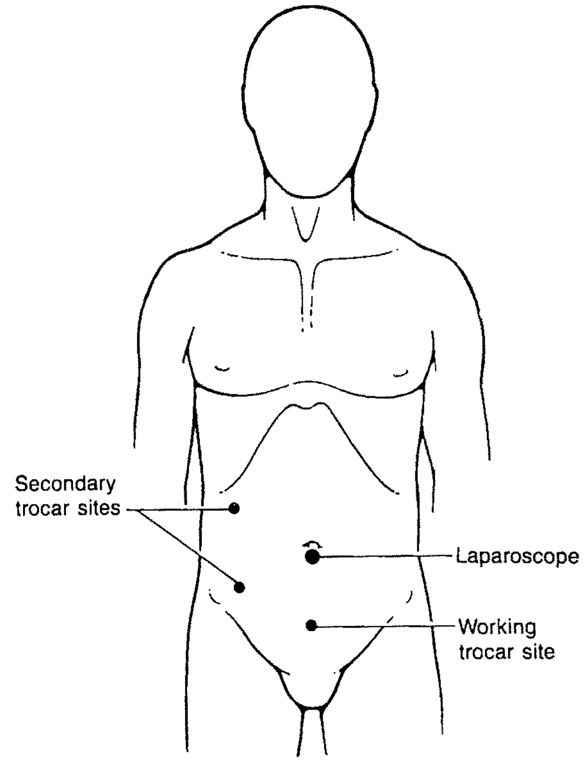

FIG. 2. Placement of trocars for laparoscopic appendectomy.

The fourth (5 mm) trocar was placed in the right upper quadrant, near the anterior axillary line. Placement of this trocar varied, depending on the location of the appendix and the patient's size. The first assistant grasped the cecum with an atraumatic grasping forceps and continued the cephalad retraction begun by the surgeon. The appendix then was grasped by the first assistant (Fig. 3A). If the appendix was so inflamed as to be difficult to grasp, it was encircled with a pre-tied chromic ligature (Endoloop, Ethicon Inc., Somerville, NJ), and the long tail of this ligature was used for retraction (Fig. 3B). The first assistant manipulated the appendix until it and its mesentery were clearly displayed for the surgeon.

The surgeon made a window in the appendiceal mesentery with an alligator-tipped forceps. Clips (EndoClip; US Surgical Corporation, Norwalk, CT) were applied (Fig. 3C) and the mesentery was divided with hook scissors. The mesentery then was divided serially until the base of the appendix was disclosed. The base was carefully inspected to confirm that the juncture of the appendix with the cecum had been defined. The appendix was ligated with two chromic ligatures at the base of the cecum, and a third ligature was placed approximately 1 cm distal (Fig. 3D). The appendix was divided with scissors and removed through the working trocar.

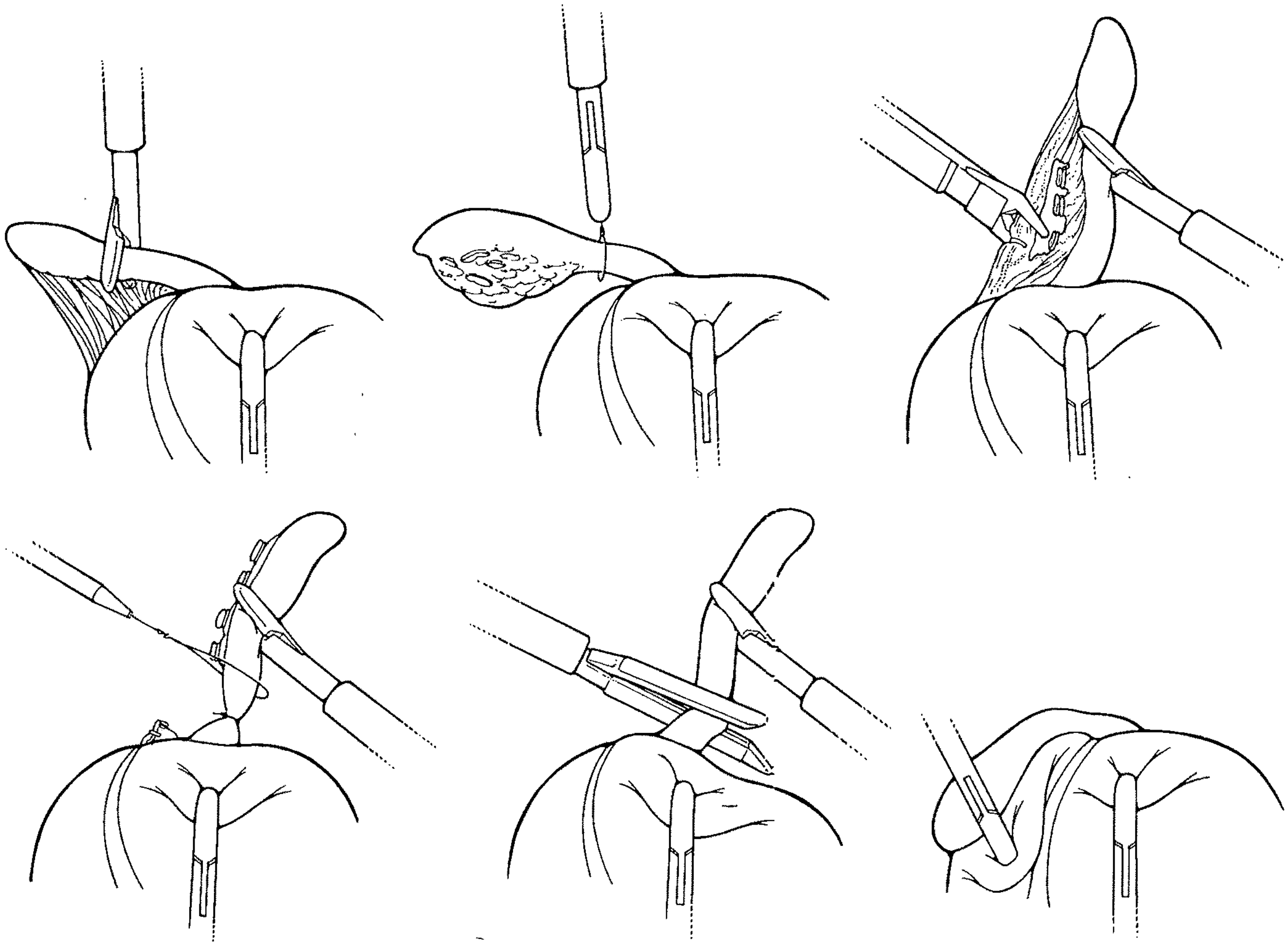

FIG. 3. (A, top left) The appendix is grasped by the first assistant while traction of the cecum cephalad maintains exposure. (B, top center) A very inflamed and rigid or friable appendix may be handled more easily by encircling it with a pre-tied chromic ligature. The first assistant grasps the tail of the ligature rather than the appendix. (C, top right) The mesentery is serially clipped and divided by the surgeon. (D, bottom left) Two pre-tied chromic ligatures are placed at the base of the appendix where it merges with the cecum and a third ligature is placed approximately 1 cm distally. (E, bottom center) Alternatively, an endoscopic stapler is placed across the base of the appendix after the mesentery has been divided. (F, bottom right) A retrocecal appendix may be exposed by incising the white line and rolling the cecum cephalad and medially.

The stump of the appendix and the appendicular artery then were carefully inspected. If the clip on the appendicular artery seemed insecure, it was secured with an additional chromic ligature. The appendiceal stump was not cauterized nor was an attempt made to invert it.

When the stapling device (Endo-GIA; US Surgical Corporation, Norwalk, CT) was used, a 12-mm port was used for the working trocar. A window was made in the mesentery at the base of the appendix. The stapler was loaded with a 1.0-mm cartridge and fired across the mesentery, securing it with a triple row of staples and dividing it. The stapler was reloaded with a 1.5-mm cartridge and fired across the base of the appendix (Fig. 3E). The appendix was removed through the 12-mm port.

When the appendix was retrocecal, mobilization and exposure was accomplished by sharply incising the white line lateral to the cecum and rolling the cecum medially and cephalad (Fig. 3F).

Monopolar electrocautery was used for hemostasis. The operative site and pelvis were copiously irrigated with saline at the conclusion of the procedure. Neither antibiotics nor heparin were added to the irrigation solution. No drains were used. Trocar sites were inspected for bleeding at the conclusion of the procedure. The fascia of the large (10 to 12 mm) trocar sites was closed with Vicryl (Ethicon); the fascia of the 5-mm trocar sites was left open. The skin was closed with an absorbable subcuticular suture.

All patients received a single dose of a cephalosporin antibiotic (cefoxitin) intravenously on call to surgery and at least two more doses in the immediate postoperative period. Patients in whom purulent-appearing fluid was

TABLE 1. *Laparoscopic Diagnosis, Treatment, and Pathologic Diagnosis*

Laparoscopic Diagnosis	No.	Treatment	Pathologic Diagnosis	No.
Acute salpingitis	1	Antibiotics	—	
Possible appendicitis	3	Laparoscopic appendectomy	Fibrosis	1
			Chronic inflammation	1
			Normal appendix	1
Acute appendicitis	9	Laparoscopic appendectomy	Acute appendicitis	8
			Appendix with fecalith	1
	1	Open appendectomy	Acute appendicitis with perforation	1
Perforated sigmoid diverticulitis	1	Hartmann's procedure	Perforated diverticulitis	1
Torsion of ovarian cyst	1	Laparoscopic cystectomy	Acute torsion of dermoid cyst	1

noted in the abdomen were continued on antibiotics until operative culture results were available. Antibiotics were discontinued when patients were clinically well and had been afebrile for 24 hours. The Foley catheter and nasogastric tube were removed in the recovery room. Antiemetic agents were not routinely used, because of concern that complications might be masked.

Results

Patient Population and Presentation

There were nine men and boys and seven women and girls, with ages ranging from 16 to 47 years (mean, 27.2 years). Patient weights ranged from 46 to 122 kg (mean, 71.8 kg). All patients had right lower quadrant pain of at least 24 hours' duration. Three patients had a history of prior similar attacks that resolved spontaneously. Preoperative temperatures ranged from 37.1 to 39.4 C (mean, 37.9 C) with total white blood cell counts ranging from 6000 to 26,000/mm^3 (mean, 13,400/mm^3). Radiographic findings were nonspecific, and no fecaliths were seen.

Findings at Laparoscopy and Surgical Management

A diagnosis was established at laparoscopy in all 16 patients. The laparoscopic diagnoses, treatment, and pathologic diagnoses are detailed in Table 1. A presumptive diagnosis of possible or definite appendicitis was made at laparoscopy in 13 patients. Laparoscopic appendectomy was successfully achieved in all 12 patients in whom it was attempted; three of these patients had retrocecal appendices and the other nine had the appendix lying intraperitoneally. One patient had a gangrenous, perforated appendix. This patient was an insulin-dependent diabetic and was the fifth patient in the series; the attending surgeon judged that open management would be safer than LA, and did not attempt LA.

Three patients had laparoscopic diagnoses other than acute appendicitis. Two of these patients were managed laparoscopically. One patient had salpingitis with a normal appendix and underwent diagnostic laparoscopy only. A second patient had an acute torsion of a large dermoid cyst of the right ovary. The infarcted, torsed adnexa was divided using the endoscopic stapling device. The working trocar site had to be enlarged to deliver the cyst. The third patient had a normal appendix at laparoscopy, with an abnormal appearing sigmoid colon and free pus in the pelvis. A presumptive diagnosis of colonic perforation, possible diverticulitis, was made. Laparotomy with Hartmann's procedure was performed and subsequent pathologic examination disclosed perforated diverticulitis.

Conversion Rate and Complications

Two of the 16 patients underwent laparotomy (12.5%; perforated appendix, perforated sigmoid diverticulitis). In addition, two patients required extension of a trocar site. One of these patients had persistent muscle bleeding from the right lower quadrant trocar site, visible at laparoscopy. It was treated by exploration of the trocar site and ligation of a muscle bleeder. The second patient had a 10-cm torsed dermoid cyst containing hair and semisolid material. The cyst could not be decompressed sufficiently to deliver it through an existing trocar site. The working trocar site was extended as a minilaparotomy to allow the cyst to be delivered without soilage of the peritoneal cavity. Thus a total of four patients (25%) of the original 16 required either formal laparotomy for management of their pathology, exploration of a trocar site for bleeding, or extension of a trocar site.

Complications occurred in four of 16 (25%) laparoscopic procedures (Table 2). No patients required reoperation. Although one patient developed a small stitch

TABLE 2. *Complications Occurring in 14 Patients Treated Laparoscopically*

Complication	Management and Outcome
Fever, abdominal pain 2 weeks after operation	Computed tomography scan negative for abscess, IV antibiotics × 1 wk, resolved
Trocar site bleeding	Recognized at laparoscopy, trocar site explored, vessel ligated
Unilateral pulmonary edema in recovery room	Positive pressure ventilation (<12 hr), resolved
Stitch abscess at trocar site	Suture removed in clinic, resolved

abscess, there were no significant wound infections and no intra-abdominal abscesses. There were no deaths.

Operative Time

Operative times for the 14 patients treated laparoscopically ranged from 53 to 142 minutes (mean, 96.6 minutes). In the 12 patients who underwent LA, the mean operative time was 95.7 minutes (range, 53 to 142 minutes). The operative times did not appear to decrease with team experience (Fig. 4).

Postoperative Stay and Return to Normal Activities

Mean postoperative stay in the 14 patients treated laparoscopically (12 LA, 1 diagnostic laparoscopy, 1 ovarian cystectomy) was 2.4 days (range, 1 to 4 days). In the 12 patients who underwent LA, the mean stay was 2.5 days (range, 2 to 4 days). At the time of the first postoperative visit, between 1 and 2 weeks after surgery, all patients reported that they had returned to normal activities.

Resident Training

All procedures were performed by chief residents with an attending surgeon as first assistant. A total of six chief residents participated. Each chief resident had performed a mean of eight laparoscopic cholecystectomies (range, 1 to 17) at the time of performance of first LA. Four chief residents each performed one LA, and two chief residents each performed four LAs. As confidence was gained with the technique, the number of patients in whom the laparoscopic approach was selected preferentially increased, as compared with those in whom open appendectomy was chosen at the time of presentation (Fig. 5). During the first year of the study, three laparoscopic and 14 open operations for right lower quadrant pain were performed in the gastrointestinal surgical service at University of Mississippi Medical Center; in contrast, during the second 10 months of the study, there were 11 laparoscopic operations and one open operation done.

Discussion

Laparoscopic appendectomy was first described by Semm, and was initially limited to incidental appendectomy performed at the time of gynecologic laparoscopy or to appendectomy for chronic appendicitis or endometriosis.[1-4] As familiarity developed, the technique was further refined and indications extended to equivocal cases of appendicitis and finally to known appendicitis.[5-19]

The surgical technique is now well developed, and several methods have been described for both antegrade and retrograde appendectomy. The original technique of Semm most closely mimicks the open technique used by most American surgeons.[1,3,14] After careful exposure of the appendix, the appendiceal mesentery is ligated and divided. The appendix is ligated and the stump invaginated by purse string or Z-stitch.[14] Fallopian tube ligation bands and clips have been described as alternative methods to secure the appendiceal stump.[5,10,18] The clip may have some advantage in thickened appendices.[18] Most laparoscopic surgeons, however, have preferred to ligate the base of the appendix with a Roeder knot, generally in the form of a pre-tied, commercially available chromic

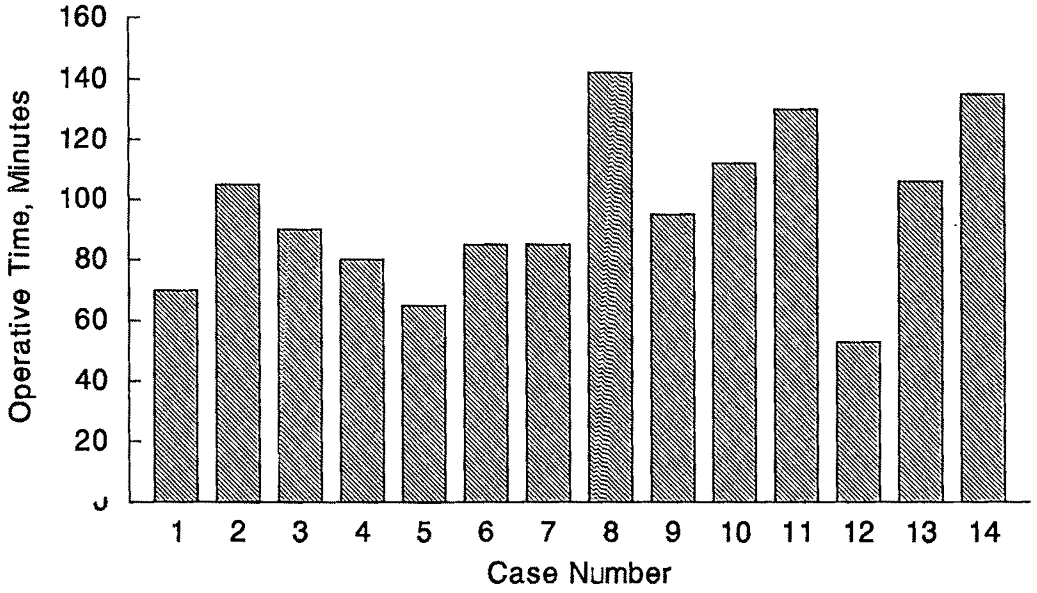

FIG. 4. Operative time for 14 sequential laparoscopic procedures for right lower quadrant pain. Two laparoscopic procedures that were converted to formal laparotomy are not included in the graph.

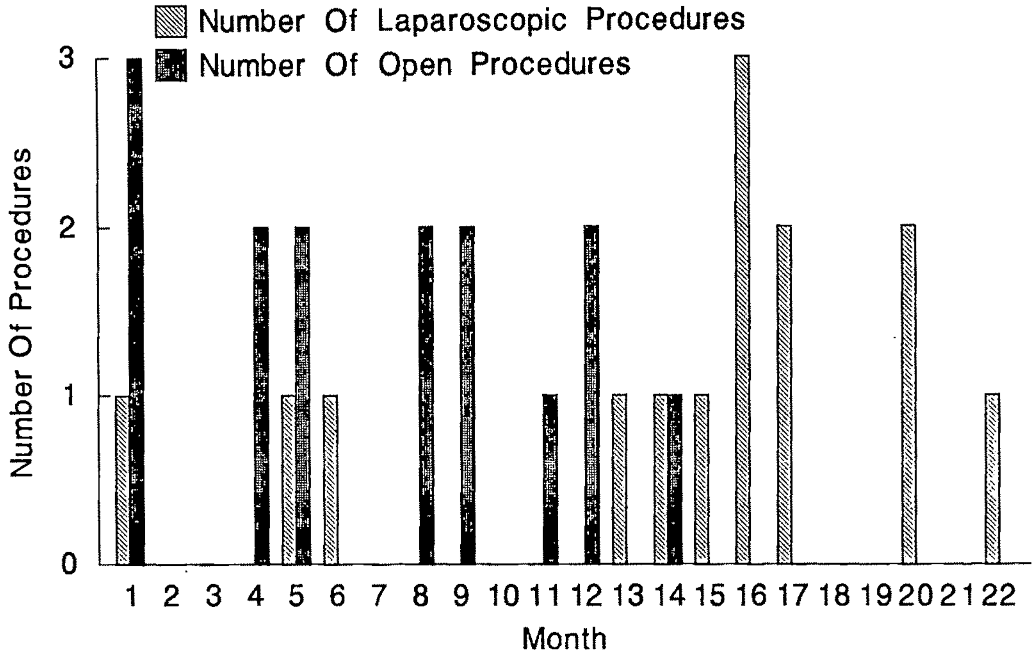

FIG. 5. Laparoscopic and open operations for right lower quadrant pain performed on one teaching service during the study period. Two of the laparoscopic procedures detailed in this report were performed on other teaching services by chief residents under the direction of attending surgeons (CSC, FM) involved in this study. Those two procedures do not appear in this graph.

ligature as we have used.[15,16] Closure using an endoscopic stapling device (Endo-GIA; US Surgical Corporation, Norwalk, CT) has been described and was used in one of our cases.[17] Inversion of the stump can be performed by laparoscopic suturing.[1,3,14] It is generally omitted because comparative studies of stump inversion during open appendectomy have failed to demonstrate any advantage[20] and because suturing is still technically difficult for most laparoscopic surgeons. Although the procedure can be done with three punctures and has been described with two, the use of four punctures allows better control by the attending surgeon.

The negative appendectomy rate in most series of open appendectomies ranges from 20% to 30% in adults.[21-24] It may be higher in the subset of young women of reproductive age, in whom the differential diagnosis of gynecologic pathology can be difficult.[25-27] Berry and Malt,[24] in a detailed review of multiple large published series of appendectomies, showed that the perforation rate increases linearly with diagnostic accuracy. The generally accepted negative appendectomy rate of 20% to 30% for adult patients recognizes this trade-off.[21] Laparoscopy has been advocated as a means of decreasing the negative appendectomy rate in patients, particularly female patients, with equivocal signs of appendicitis.[25-28] An initial series from the pediatric age group of 32 patients with suspected appendicitis demonstrated two false-negative laparoscopies and one false-positive.[25] In an early series, 42 of 46 laparoscopic examinations were successful, but the appendix was visualized directly in only four patients.[28] Indirect signs of appendicitis such as adherence of the omentum to the region of the appendix, cecal inflammation, or the presence of turbid fluid in the pelvis were used as indicators of acute appendicitis.[28]

Operative laparoscopic techniques now in common use were not available then. Because laparoscopy as performed in the United States requires general anesthesia, and because open surgery was required if appendicitis or, indeed, a surgical gynecologic problem was found, this method did not gain widespread popularity. The availability of laparoscopic instruments and techniques for appendectomy, management of ruptured ectopic pregnancies, ovarian cysts, and so on renders this approach more promising. In our series, the appendix was successfully visualized and the pathology identified in all patients. The clear visualization of the upper abdomen, pelvis, and adnexae that is obtained laparoscopically is in contrast to the limited view obtained through the standard McBurney or Rocky-Davis incision. As in laparoscopic cholecystectomy, this advantage is most appreciated in the obese patient. Two of our patients weighed more than 100 kg; one underwent successful LA and the second laparoscopic ovarian cystectomy. In our institution, ruptured ectopic pregnancy is now managed laparoscopically. Two other gynecologic conditions (salpingitis and a torsion of an ovarian cyst) were identified and managed laparoscopically in our series. Laparoscopy allows thorough inspection of all four quadrants of the abdomen. In our series, three patients (18.8%) had other causes for their pain accurately determined at laparoscopy.

The diagnosis of appendicitis is not always certain at laparoscopy, as during open appendectomy.[22-28] One disadvantage of laparoscopy is the inability to feel structures and judge pathology by touch. Palpation with instruments and probes only partially compensates. No patient in our series had a missed diagnosis or has returned with inflammatory bowel disease.

Our philosophy has been to perform the same operation through the laparoscope, for the same indications, that we would perform open. Thus, appendectomy was performed in cases in which no cause could be found for the pain and in which the appendix appeared normal, just as it would have been during open surgery. Such a policy will not diminish the rate of "cold" appendices removed, which was four of 12 (33%) in our series. Only one of these was histologically normal (8.3%), however. That significant morbidity can follow a negative open appendectomy was emphasized by Chang et al.,[29] and it remains to be seen whether laparoscopic appendectomy will have an acceptable morbidity rate when the appendix is histologically normal.

Wound infection remains a significant complication of open appendectomy, averaging 8.5% to 20%.[22-24] In contrast, Pier and Götz reported only three wound infections in a series of 625 LAs.[15] In the only comparative series published to date, the wound infection rate was 11% in open and 4% in laparoscopic appendectomies, and the only wound infection after LA occurred in a patient with a gangrenous appendix who was converted to open appendectomy.[19] When the appendix is withdrawn through the trocar or through an appendix extractor during LA, there is no contact of infected material with the subcutaneous fat. Although one suture abscess occurred, there were no wound infections in our small series. We remain concerned about the possibility of fascial infection, however, and would consider leaving the skin open in the event of fascial contamination.

Operative times did not diminish with experience in our series, despite increasing confidence in the technique as shown by increased use during the second year of the study. In fact, our operative times are higher than those quoted by most authors.[12,15,19] We believe that this was related to the infrequent nature of these procedures (averaging less than one per month over the study period), that most cases were done on the evening or night shift with operating room personnel unfamiliar with equipment and supplies, and the unpredictable nature of the anatomy and findings. Involvement of residents as surgeons and camera drivers and turnover of resident teams, with six chief residents being trained during the study period, may have contributed to longer operative times as well. We regard these factors as inevitable within the training environment.

As confidence was gained with the technique, we performed an increasing number of our cases laparoscopically. The fifth case in the series, managed by open appendectomy when a gangrenous appendix was visualized, would now be treated laparoscopically in the opinion of the attending surgeon.

Postoperative stay averaged 2.5 days. Most of our patients went to surgery at night. Although all started clear liquids the morning after surgery, most were unable to tolerate solid food until the second postoperative day. This postoperative stay compares favorably with that reported for open appendectomy uncomplicated by wound infection, which significantly prolongs hospital stay.[19,22-24] No patient in our series developed a significant wound infection and no patient remained longer than 4 days in hospital. It is difficult to compare this stay with published series of open appendectomies, most of which date from times when patients were hospitalized longer than currently.[22-24] Mean hospital stays in those series range from 5.3 days to 9.1 days and are probably not representative of current practice.[22-24] In McAnena et al.'s series,[19] the mean stay after open appendectomy was 4.8 days, compared with 2.2 days after laparoscopic appendectomy. This latter postoperative stay is quite comparable to our series. All of our patients were back to normal activities at the time of their first postoperative visit, between 1 and 2 weeks after surgery.

One complication in our series, trocar site bleeding, is unique to laparoscopy. It was recognized during surgery in our patient, and simple extension of the trocar site with direct suture of the bleeding vessel controlled the bleeding. Although Leahy has recommended "laparoscopic transillumination" as a method for visualization of the inferior epigastric vessels, most of our patients were too obese for this to be feasible.[10] We believe that this problem can be minimized by placement of trocars lateral to the rectus sheath. The three other complications, a phlegmon, a suture abscess, and unilateral pulmonary edema (possibly drug-related), are not unique to laparoscopy.

The procedure that we use for LA allows a chief resident to perform the critical steps of the operation with full control being maintained by the first assistant. For this reason, one trocar (the working trocar) was used by the surgeon, and two trocars were used by the first assistant. The procedure could easily be modified to allow a two-handed approach by the surgeon. Reserving two trocars for the attending surgeon has facilitated teaching the operation to our chief residents, especially because many of these procedures were done late at night.

The reaction of junior residents to the increasing encroachment on their cases (first cholecystectomy and then appendectomy) has been interesting. By making the first- or second-year resident an integral part of the team (camera driver) from the beginning, resentment has been minimized. In our program, laparoscopic cholecystectomy is starting to be a third- or fourth-year resident case rather than a chief resident case. This has helped to minimize junior resident anxiety. In addition, LA has been primarily performed on one of three general surgery services, allowing experience with open techniques to be gained on the other two services.

We have noted several pitfalls and difficulties in laparoscopic appendectomy:

1. If the patient is positioned on the operating table with the arms outstretched, it will be difficult for the first assistant and camera operator to stand comfortably. The arms should be tucked at the patient's side.
2. Placement of the trocars too close together will make it difficult for the surgeon and first assistant to work together without interference. This is most likely to be a problem in the small, slender patient.
3. Troublesome bleeding can result if trocars are placed through the rectus muscle or inferior epigastric vessels. Avoid this by placing trocars lateral to the edge of the rectus sheath.
4. If the appendix is extremely mobile, it may be pulled into the upper abdomen by the first assistant. This change of field makes eye-hand coordination difficult for the surgeon and decreases the space available for operating. It also forces the camera operator to move toward the foot of the table, crowding the surgeon. This can be recognized by noting the direction in which the laparoscope is pointing. The laparoscope should point into the right lower quadrant. This is easily corrected by pulling the appendix back down into the lower abdomen.
5. A very long appendix may be difficult to retract because the grasper holding the appendix is pushed up against the underside of the abdominal wall. Such an appendix must be regrasped closer to the base, and the tip allowed to dangle, so that the base of the appendix at the cecum can be accurately identified.

In summary, we believe that laparoscopic appendectomy can be safely performed within the context of a training program. Surgical chief residents who are experienced in the techniques of operative laparoscopy, including laparoscopic cholecystectomy, can perform the procedure with the assistance of an experienced attending surgeon. Diagnostic accuracy is excellent and postoperative complications are acceptable. In particular, wound infection rates may be lower in LA.[15,19] Operative time will probably remain higher than that required for open appendectomy, and postoperative stay, largely determined by length of antibiotic treatment, is comparable.

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DISCUSSION

DR. THOMAS R. GADACZ (Augusta, Georgia): Dr. Ochsner, Dr. Jones, it is a pleasure to discuss Dr. Scott-Conner's paper on laparoscopic appendectomy, and I appreciate a copy of the manuscript. We have had experience with this procedure, but I would like to limit my comments to her paper.

I have two technical and a few general questions. You used four cannulas for the procedure. How important was the right axillary cannula and did it help with exposure? The second technical question is the method of extracting the appendix. We prefer to extract, particularly the large, gangrenous appendix, from the abdomen in a latex bag to prevent contamination of the cannula track, especially if it does not fit in the cannula. Please comment on methods to remove the appendix to prevent wound infection.

The three general questions I have are: What is the role of laparoscopic appendectomy, particularly in children? In this group, it may be better to perform a standard appendectomy, particularly when the diagnosis is much more certain and the time to perform the procedure much less. Would diagnostic laparoscopy be indicated in patients with lower abdominal pain at an earlier stage of the disease, thus decreasing the period of observation? And the final question is, how would the availability of laparoscopy influence your use of computed tomography to diagnose lower abdominal pain? I enjoyed the presentation and congratulate you on a good study.

DR. LESTER WILLIAMS (Nashville, Tennessee): Dr. Ochsner, Dr. Jones, Members, Ladies, and Guests, I asked to discuss this because our experience at Vanderbilt and St. Thomas has been exactly the same as that presented. But I really wanted to ask the question that we now get regularly in our teaching conferences. We almost never discuss the technique or this week's gadget with respect to laparoscopic appendectomy, but want to know what should we do and when should we do it. We cannot come to consensus if diagnostic laparoscopy has been done for apparent appendicitis and the appendix is normal; should we stop or should the appendectomy be continued? There are some data that suggest we should stop. And, in fact, the British have a well-done series in which they now suggest that every woman of childbearing age who is being operated on for appendicitis should routinely have diagnostic laparoscopy and, if they do not find appendicitis, should have nothing further done. Would you suggest that these are reasonable points of view now that we know the procedure can be done, can be done safely, and probably can be done in most patients for whom appendectomy is appropriate? Thank you.

PRESIDENT OCHSNER: Dr. Scott-Conner, would you close, please? And I would like to ask you a question. Why not use an antibiotic bacteriocidal solution, because you are obviously contaminating that area of the stomach?

DR. CAROL E. H. SCOTT-CONNER: (Closing discussion): I think that is an excellent question, and I would like to address that first. Perhaps we were acting as purists and following the dictum that intravenous antibiotics timed properly are as effective or perhaps more effective than local antibiotics in prevention of the major morbidity, which is wound infection. I do not think that there is any harm in adding antibiotics to the irrigation solution. Many people do this routinely in the performance of laparoscopic cholecystectomy. We have tried to keep the procedure as simple as possible. Most of these were done after midnight with an inexperienced operative crew who did not know how to use the equipment. And so we gave intravenous antibiotics and relied on this alone.

Dr. Gadacz, we used four cannulas as a sort of security blanket for the attending surgeon. This gives the attending the maximum control over the procedure and allows that person to manipulate the appendix and the cecum to provide optimum visualization of the mesentery. This allows the procedure to be done even for the first time by a relatively inexperienced resident with minimal technical complications during the performance of the procedure. There is no question that it can be done with fewer than four cannulas, and probably most surgeons in practice around the country who take up this technique will choose to do it with three and use a two-handed technique by the operative surgeon. We did it simply for security and because it may be easier for us to expose the appendix. The use of a rubber bag to contain the appendix and minimize contamination is an excellent technique and one that we will undoubtedly employ in the future. It had not been described when we began this study, and so we struggled to deliver some of these large and inflamed appendices through first a 10-mm, and then as they became available, the 11- and 12-mm trocars. Most appendices will fit within a 12-mm trocar. The problem that we have had is that the overzealous resident will then try to remove the appendix through the trocar rather than simply withdrawing it into the trocar and removing trocar and appendix together through the abdominal wall. I think the latex bag is going to make this procedure a lot safer and minimize fascial contamination, particularly in the gangrenous appendix.

As far as the pediatric age group, I would be extremely conservative in applying this technique to children. Particularly in very small children in whom the abdominal cavity is small and the diagnosis is certain, appendectomy is a very short and safe procedure done through an incision that can be covered by a single band aid in many cases. In the chunky, muscular adolescent, however, particularly one who is active in college or high school athletics and in whom a wound infection can be a devastating problem, I think that laparoscopic appendectomy may have something to offer.

As far as laparoscopy and the timing of laparoscopy and whether it should be done earlier or whether it should be done in all women of childbearing age, we have not altered our indications for doing appendectomy so far. We have tried to adhere to the same guidelines that we would use during open surgery. We do think that there may be a role for earlier laparoscopy, particularly in women of childbearing age, in whom the rate of negative appendix is high. The stakes are also high in these women, as it has been shown that the sequelae of a perforated appendicitis may be fertility problems down the road. At this point, because we are uncertain of our laparoscopic diagnostic capability in the plus–minus appendix, we go ahead and remove the appendix. This is what we would do during open surgery. We believe that because the patient has gone through general anesthesia, and because we are not always sure whether it is minimally inflamed or a true cold appendix, we go ahead and remove it. What the complications will be of these true negative appendices and whether this procedure is justified remains to be determined. I thank the Association and I thank the discussants for their many thoughtful comments.

Selective Cholangiography

Current Role in Laparoscopic Cholecystectomy

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The initial 22-month experience with laparoscopic cholecystectomy in 400 patients employing an algorithm of selective cholangiographic evaluation is reported. Preoperative or postoperative endoscopic retrograde cholangiography was performed whenever stones were suspected clinically. Preoperative endoscopic retrograde cholangiography was performed in 44 patients (11%), in whom 14 (3.5%) had an endoscopic sphincterotomy with extraction of common bile duct stones. Intraoperative cholangiography was performed in only eight patients (2%) almost exclusively to acquire experience with the technique, and all cholangiograms were normal. Laparoscopic cholecystectomy was successfully completed in 96% of the patients. There were no deaths in this series, and major complications occurred in only 5% of patients. Two patients (0.5%) had a significant common bile duct injury that was recognized and successfully repaired at the initial operation. No late common bile duct strictures have been recognized. Six patients (1.5%) underwent postoperative endoscopic retrograde cholangiography for suspected common bile duct stones, with three patients requiring endoscopic sphincterotomy and stone extraction. This experience suggests that the use of preoperative and postoperative endoscopic retrograde cholangiography can be based on clinical presentation and laboratory evaluation and does not need to be performed routinely. Routine intraoperative cholangiography is not necessary in most patients undergoing laparoscopic cholecystectomy. The authors conclude that laparoscopic cholecystectomy can be performed safely with the selective use of cholangiography.

THE ROLE OF routine intraoperative cholangiography during cholecystectomy has been debated for years. Arguments in favor of routine cholangiography have included: (1) identification of clinically unsuspected common bile duct (CBD) stones, (2) definition of the anatomy of the extrahepatic biliary tree to prevent CBD injuries, and (3) development of experience with the technique. Currently the same arguments are being debated concerning routine use of intraoperative cholangiography during laparoscopic cholecystectomy. One factor used to support the use of routine cholangiography is the higher incidence of bile duct injuries reported in the early series of laparoscopic cholecystectomy.[1-5] Advocates of routine cholangiography have stressed that defining the biliary anatomy at laparoscopy before dividing any ductal structure will reduce the rate of significant bile duct injury.[6-8] Routine preoperative endoscopic retrograde cholangiography (ERC) also has been advocated before laparoscopic cholecystectomy.

The authors' initial bias was that laparoscopic cholecystectomy can be performed safely in most patients with selective use of preoperative and intraoperative cholangiography. We have applied the algorithm of selective preoperative ERC for patients with suspected CBD stones, using endoscopic sphincterotomy when stones were found. We have used intraoperative cholangiography rarely in our initial experience with laparoscopic cholecystectomy. This report suggests that laparoscopic cholecystectomy can be performed safely with selective use of cholangiography.

Clinical Material

Four hundred consecutive patients with symptomatic gallbladder disease underwent attempted laparoscopic cholecystectomy at the Johns Hopkins Hospital between December 1989 and October 1991. All patients were evaluated before operation by one of the authors, who established the need for cholecystectomy and completed

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a standard preoperative evaluation. During our initial months of this experience, strict patient selection criteria were applied to optimize the results during the learning phase of this procedure. Currently, however, more than 95% of patients referred to the authors undergo an attempt at laparoscopic cholecystectomy.[9]

Evaluation for CBD stones consisted of ultrasonography to define the number and size of gallstones and to determine CBD size. Preoperative serum amylase and liver function tests (serum bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase) were performed routinely. Patients were referred for preoperative ERC at the discretion of the primary surgeon on the basis of these preoperative studies.

Laparoscopic cholecystectomy was performed by standard techniques.[1,2,5,10] At least one of the authors served as the surgeon or first assistant during all of the cases. A 30° forward oblique viewing telescope was used in all cases to optimize visualization. Cephalad traction on the fundus and lateral traction on the infundibulum of the gallbladder were essential to expose and safely dissect the triangle of Calot. The dissection of the cystic duct was performed at its junction with the gallbladder infundibulum. An adequate length of the cystic duct was exposed before clipping and dividing the structure. No attempt was made to dissect the cystic duct down to its junction with the CBD. The cystic artery was then identified, doubly clipped, and divided. The electrocautery was used to dissect the gallbladder from the liver bed.

Data were prospectively collected from all patients. Follow-up was obtained on all patients either by an outpatient visit with the primary surgeon or by contact with the referring physician within 1 month of operation.

Results

Patient Population

Of the 400 patients, 293 were women (73%) and 107 were men (27%). The mean age was 47.9 years (range, 15 to 96 years). Previous abdominal operations had been performed in 28% of patients. Most procedures were lower abdominal (22%) and were primarily obstetric or gynecologic in nature. An upper abdominal incision was present in 2.8% of patients. Operations involving the umbilicus, primarily umbilical herniorrhaphy, had been performed in 2.5% of patients. Obesity, defined as at least 40 pounds above ideal body weight, was present in 25% of patients.

Symptoms

The primary indications for laparoscopic cholecystectomy are shown in Table 1. Chronic biliary tract symptoms were present in 88% of patients. In 10 patients (2.5%), chronic typical biliary symptoms were present without demonstrable gallstones. Cholecystectomy was offered to these patients after extensive workup to eliminate other causes for the symptoms. Although chronic biliary tract symptoms were present in 88% of patients, surgical referral in 18% of patients was based on a complication of cholelithiasis. Thirty patients (7.5%) presented with acute cholecystitis. In 10 of these patients (2.5%), laparoscopic cholecystectomy was attempted during the acute attack. In the remaining 20 patients (5%) laparoscopic cholecystectomy was attempted 6 to 8 weeks after the acute episode. Twenty-two patients (5.5%) presented with gallstone pancreatitis. Laparoscopic cholecystectomy was performed in eight of these patients during the initial hospitalization, whereas 14 patients had interval laparoscopic cholecystectomy performed after the index admission for gallstone pancreatitis. Symptoms of choledocholithiasis jaundice, or cholangitis were present at the time of referral in 19 of the patients (4.8%). Ten of these patients underwent laparoscopic cholecystectomy during the initial admission after successful endoscopic management of their bile duct calculi.

TABLE 1. *Indications for Laparoscopic Cholecystectomy in 400 Patients*

Presentation	N
Chronic biliary tract symptoms	352 (88%)
Calculus	342 (85.5%)
Acalculus	10 (2.5%)
Acute cholecystitis	30 (7.5%)
Previous episode	20 (5.0%)
Current admission	10 (2.5%)
Gallstone pancreatitis	22 (5.5%)
Previous episode	14 (3.5%)
Current admission	8 (2%)
Cholangitis/jaundice	19 (4.8%)
Previous episode	9 (2.3%)
Current admission	10 (2.5%)
Gallbladder polyps	9 (2.3%)

Preoperative and Intraoperative Cholangiography

Preoperative ERC was performed in 44 patients (11%). Thirty-one patients (7.8%) underwent preoperative cholangiography because of a high clinical suspicion of choledocholithiasis. Symptomatic choledocholithiasis, with gallstone pancreatitis, cholangitis, or jaundice, occurred in 24 patients, whereas seven patients underwent ERC for symptomatic gallstones with abnormal liver function tests. Fourteen of these 31 patients (45%) had CBD stones identified by preoperative ERC. An endoscopic sphincterotomy and stone extraction was performed in all 14 patients. The overall incidence of documented preoperative choledocholithiasis requiring endoscopic sphincterotomy was 3.5%. Before surgical referral, 13 patients underwent ERC for evaluation of biliary tract symptoms without clinical or laboratory evidence of choledocholithiasis. No CBD stones were identified in these patients. In nine patients, the indication for ERC was for the evaluation of typical biliary tract symptoms without documented gallstones. Four patients with known gallbladder stones underwent ERC by the referring physician in the evaluation of abdominal pain without specific indications of choledocholithiasis.

Transcystic duct cholangiography during laparoscopic cholecystectomy was performed in eight patients (2%). In six patients, intraoperative cholangiography was performed to gain experience with the technique, without other specific indications. In two patients, abnormal liver function tests were the indication for cholangiography. All cholangiograms were successfully completed without complication. No CBD stones were identified, nor did the cholangiographic findings influence the performance of the laparoscopic cholecystectomy.

Laparoscopic Cholecystectomy: Intraoperative Results and Complications

Laparoscopic cholecystectomy was successfully completed in 383 of the 400 patients (95.8%). The reasons for conversion to open cholecystectomy are shown in Table 2. Significant inflammation precluding laparoscopic cholecystectomy was encountered in nine patients. Three patients required conversion to open cholecystectomy because of inflammation during an attack of acute cholecystitis. The single patient requiring conversion due to bleeding was also a patient with acute cholecystitis that occurred after a lower extremity vascular reconstruction. This patient had been systemically heparinized, and although preoperative coagulation studies were corrected, bleeding from the liver bed required laparotomy. The patient, who was anemic before surgery, received 2 units of packed red blood cells. The overall success rate in patients undergoing laparoscopic cholecystectomy for acute cholecystitis was 60% (6/10). None of the 20 patients with a history of recent acute cholecystitis required conversion to open cholecystectomy. Thus, the overall success of laparoscopic cholecystectomy with a history of acute cholecystitis was 87%. Six patients requiring conversion did not have clinically apparent acute cholecystitis. A previous endoscopic sphincterotomy had been performed for bile duct stones in two of these six patients, however.

TABLE 2. *Reasons for Conversion to Open Cholecystectomy in 17 Patients*

Reason	N
Inflammation	9 (2.3%)
Common bile duct injury	2 (0.5%)
Abnormal anatomy	2 (0.5%)
Bleeding	1 (0.3%)
Injury to accessory hepatic duct	1 (0.3%)
Trochar injury to small bowel	1 (0.3%)
Obesity	1 (0.3%)

Abnormal anatomy in two patients, including an intrahepatic gallbladder and a double cystic duct, required conversion to open cholecystectomy. A morbidly obese patient, weighing more than 320 pounds, required conversion to an open cholecystectomy because of inability to adequately retract and expose the gallbladder infundibulum and cystic duct.

Intraoperative complications led to conversion to an open procedure in the remaining four patients. Major bile duct injury occurred in two patients. Both injuries occurred between cholecystectomy numbers 100 and 200 in our series. One patient had significant chronic inflammation with scarring of the triangle of Calot. During initial dissection in this area and before the cystic duct could be identified, leakage of bile was visualized, and the patient was converted to an open procedure. At laparotomy, it was determined that the patient had a low hepatic duct bifurcation with a short cystic duct inserting into the right hepatic duct. The right hepatic duct was injured at the hepatic bifurcation. Immediate reconstruction was performed with a Roux-en-Y bilateral hepaticojejunostomy constructed over transhepatic stents. The patient had no postoperative complications. At 14 months after reconstruction, her biliary stents have been removed, and the patient is asymptomatic with normal liver function tests.

The other major bile duct injury was a transection of the CBD. Although no significant inflammation or difficulty during dissection was encountered, a structure suspected of being the cystic duct was doubly clipped and divided. Further dissection showed the divided structure to be the CBD. After recognition of the injury, the patient was opened, and the bile duct was reconstructed with a Roux-en-Y hepaticojejunostomy over a T-tube in the common hepatic duct. The patient is now 12 months after the reconstruction and is asymptomatic. The T-tube has recently been removed with no evidence of a postoperative stricture. In the remaining patients, there have been no late postoperative bile duct injuries recognized, and no bile duct strictures have occurred in subsequent follow-up.

A partial-thickness incision in a segmental hepatic duct occurred during cutting of the cystic duct in one patient. Concern about the nature of the injury necessitated conversion to open cholecystectomy. A cystic duct cholangiogram identified an intact hepatic duct bifurcation and was otherwise normal. The injured duct was less than 2 mm in size, and it was ligated. The patient recovered without sequelae. The final intraoperative complication was an injury to a loop of small bowel during trochar placement. The patient had a history of two previous lower abdominal operations, including a hysterectomy and an appendectomy for ruptured appendicitis. Significant adhesions to the anterior abdominal wall may have precluded successful laparoscopic cholecystectomy; however, the use of the Hassan cannula may have prevented the enterotomy. The patient underwent small bowel repair and open cholecystectomy and had an uncomplicated recovery.

Postoperative Complications

There were no deaths in the series. All complications of laparoscopic cholecystectomy are shown in Table 3. The overall complication rate in this series is 9.3%. Major complications requiring either conversion to open cholecystectomy, reoperation, major postoperative intervention, or significant prolongation of hospital stay occurred in 20 patients (5%). Minor complications occurred in 17 patients (4.3%). The most frequent complication was urinary retention, which delayed hospital discharge in 10 patients.

Six patients (1.5%) were readmitted after discharge with symptoms of abdominal pain and abnormal liver function tests, suggesting a retained CBD stone. Endoscopic retrograde cholangiography was performed on all six patients, with retained CBD stones identified and extracted in three patients. In the other three patients, no stone was identified, the symptoms resolved, and the liver function abnormalities normalized. Two of these six patients with retained CBD stones had a preoperative ERC performed. One patient had a preoperative CBD stone removed after an endoscopic sphincterotomy. The patient underwent successful laparoscopic cholecystectomy, but returned 5 days after operation with abdominal pain and jaundice. Repeat ERC showed a CBD stone, which was extracted without a second sphincterotomy. The final patient had a negative preoperative cholangiogram. The only complication of ERC performed either before or after operation was a single episode of pancreatitis after a sphincterotomy and stone extraction.

TABLE 3. *Complications of Laparoscopic Cholecystectomy*

Complication	N
Intraoperative	
Major bile duct injury	2 (0.5%)
Enterotomy due to trochar injury	1 (0.3%)
Accessory bile duct ligation	1 (0.3%)
Bleeding (requiring blood transfusion)	1 (0.3%)
Dental injury during intubation	1 (0.3%)
Postoperative	
Urinary retention	10 (2.5%)
Retained common bile duct stone	6 (1.5%)
Cystic duct leak	5 (1.3%)
Omphalitis	3 (0.8%)
Umbilical wound infection	2 (0.5%)
Peritonitis	2 (0.5%)
Bleeding	1 (0.5%)
Pulmonary embolus	1 (0.5%)
Umbilical hernia	1 (0.3%)

TABLE 4. *Length of Stay After Successful Laparoscopic Cholecystectomy in 383 Patients*

Length of Stay	N
Outpatient	1 (0.3%)
1 day	304 (79%)
2 days	51 (13%)
>2 days	27 (7%)

A postoperative cystic duct leak occurred in five (1.3%) of the 383 patients completing laparoscopic cholecystectomy. Three of the five leaks were recognized within 36 hours of laparoscopic cholecystectomy. Hepatobiliary radionucleotide scanning confirmed the leak at the cystic duct in all three patients, and immediate laparotomy and ligation of the cystic duct stump was performed. The patients recovered without complications. One patient was readmitted 5 days after discharge with bilious ascites. Endoscopic retrograde cholangiography demonstrated a cystic duct leak. An endoscopic stent was placed; however, the bile leak persisted, and laparotomy and ligation of the cystic duct stump was performed. The final patient developed a subhepatic collection, associated with a fever, which was percutaneously drained. After 48 hours, the drainage became bilious. A sinogram through the drainage catheter demonstrated a cystic duct leak. A percutaneous transhepatic biliary catheter was placed, and the leak closed spontaneously. The patient recovered without further complication, although the postoperative stay was 30 days in duration.

Two patients developed postoperative abdominal pain, tenderness, and fever. No evidence of a bile leak could be demonstrated, and the patients recovered with a course of intravenous antibiotics. After hospital discharge, five patients have developed wound complications. Three developed periumbilical cellulitis that responded to antibiotics. Two patients developed a deep periumbilical wound infection that required the incision to be opened and local wound care. One patient returned several months after laparoscopic cholecystectomy with a periumbilical incisional hernia. The final technical complication was a young man with chronic renal failure on hemodialysis, who underwent an uneventful laparoscopic cholecystectomy. The hematocrit on postoperative day 1 decreased from 21% to 15%. Computed tomography suggested a subhepatic hematoma. The patient received 2 units of packed red blood cells and recovered without further problems.

The length of hospital stay for laparoscopic cholecystectomy is shown in Table 4. Most of patients were discharged on the first postoperative day, often less than 24 hours after surgery. The range of hospitalization was 0 to

30 days. The mean length of hospital stay in the 17 patients requiring conversion to open cholecystectomy, including those sustaining bile duct injury, was 6.7 days. Seven patients were readmitted after initial discharge for complications as discussed above.

Discussion

Laparoscopic cholecystectomy is now the treatment of choice for most patients with symptomatic gallbladder disease. The overall results and complications from several series numbering into the thousands are now available.[1-8,11-13] From these initial reports, the incidence of major bile duct injury may be as high as two to five times that of open cholecystectomy. The actual rate of bile duct injury may be even higher, in that most early reports have been from centers with a large experience with the procedure. This increased rate of bile duct injury may simply reflect the learning curve associated with a new technique. It is possible, however, that the technique of laparoscopic cholecystectomy, with early division of the cystic duct, may be inherently more dangerous than traditional cholecystectomy. This final possibility has led a number of authors to stress the necessity of routine operative cholangiography to prevent bile duct injuries.[6-8]

Those who favor routine use of intraoperative cholangiography report numerous anatomic anomalies found by cholangiography where recognition has avoided potential complications.[6-8] However, the significance of such findings is unclear, as is the proof that their recognition truly prevents injury. Bile duct injuries have been reported despite the performance of intraoperative cholangiography.[6-8,12] Furthermore, bile duct injuries may result from the instrumentation necessary to perform operative cholangiography. The most serious bile duct injury, that of complete transection of the CBD, is affected little by the current technique of intraoperative laparoscopic cholangiography. With most techniques, the proximal aspect of the duct, which is to be cannulated, is clipped before creating a small incision in the duct to insert the cholangiocatheter. If, indeed, the duct that is clipped or incised is the CBD, an injury has already been created, and some form of repair or reconstruction will be necessary.

The recognition of a short cystic duct is one abnormality frequently cited as an important variant that can be recognized by operative cholangiography. It is our belief that the key point in avoiding injury in such cases is beginning the dissection at the junction of the gallbladder infundibulum with the cystic duct. All ductal structures to be clipped and divided must have this relationship clearly defined. The use of the 30° telescope may improve visualization of the critical anatomy of the cystic duct–CBD junction.

The incidence of major bile duct injury in this series was 0.5%. These results are consistent with the incidence of bile duct injury in most other series either using routine or selective operative cholangiography. One of the injuries in this series occurred before cholangiography could have been performed. With the other injury, it is unlikely that operative cholangiography would have altered the management, because the proximal aspect of the bile duct would have already been clipped to perform the study. Both injuries in this series were recognized intraoperatively, and immediate biliary reconstruction was performed. Intraoperative recognition of a bile duct injury avoids the potential for postoperative biliary fistulas or sepsis. In addition, repair of the biliary tree can be done in an operative field without significant inflammation or adhesions.

Advocates of routine intraoperative cholangiography cite the detection of bile duct stones as the final indication for its use. This issue has been addressed extensively in reports from the prelaparoscopic cholecystectomy era, and these data remain valid now. The results from studies addressing the role of routine intraoperative cholangiography in the open cholecystectomy era report an incidence of unsuspected CBD stones ranging from 1.2% to 12.4%,[14-18] Large series of cholecystectomies without cholangiography report an incidence of residual stones as low as 0.3%.[19-21] Furthermore, the incidence of false-positive cholangiograms of 2% to 16%[17,22-24] may lead to unnecessary conversion to open cholecystectomy or postoperative investigations to search for stones.

The management of CBD stones during laparoscopic cholecystectomy presents a significantly different problem than traditional cholecystectomy. In the open procedure, if bile duct stones are recognized cholangiographically, a CBD exploration or transduodenal procedure can be performed at the same time, with only a minimal increase in morbidity rate. Although scattered reports of transcystic duct exploration or even formal common duct exploration have recently appeared,[25-27] the potential for serious bile duct injuries with such procedures is high, especially with a nondilated biliary system.[28]

The problem of choledocholithiasis, as well as concern for bile duct injury, has led for a call for routine preoperative ERC in some centers. It has been our practice, however, to selectively evaluate the biliary tree with preoperative ERC. Patients were selected for preoperative cholangiography on the basis of clinical presentation and preoperative liver function tests. The patients in this series represent a wide spectrum of biliary tract disease, including complications of CBD stones, such as gallstone pancreatitis (5.5%) and cholangitis or jaundice (4.8%). Overall, only 44 patients in this series (11%) underwent preoperative ERC. Yet, if only those studies obtained by the primary surgeon for preoperative evaluation for possible CBD stones are considered, then the preoperative cholangiography rate was only 7.8%, with 45% of these procedures finding choledocholithiasis. Using only selective preoperative cholangiography and rarely using intraoperative cholangiography (after an initial learning experience), we report only a 1.5% incidence of suspected retained CBD stones (with only 0.75% actually documented by a positive postoperative cholangiogram). These results compare favorably with studies of both laparoscopic and open cholecystectomy using routine cholangiography.

In summary, laparoscopic cholecystectomy can be performed safely without routine use of cholangiography. The incidence of bile duct injury in this series compares favorably with other reports in the literature. These results serve to support the role of careful dissection and visualization of ductal structures before division and suggest that intraoperative cholangiography is not necessary. The selective use of preoperative and postoperative cholangiography, based on clinical presentation, can successfully manage choledocholithiasis without significant complications, while still allowing completion of laparoscopic cholecystectomy in up to 95% of patients. We conclude that laparoscopic cholecystectomy can be performed safely with selective use of cholangiography.

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DISCUSSION

DR. C. RANDLE VOYLES (Jackson, Mississippi): I wholeheartedly agree with the conclusion that operative cholangiography should not be done on a routine basis to (1) prevent bile duct injury or (2) identify common duct stones. In a personal series of over 600 laparoscopic cholecystectomies, I have had no duct injury or retained stone in patients selected not to have operative cholangiography.

However, we must emphasize that endoscopic sphincterotomy has a well-documented morbidity rate of about 8%. We have seen pancreatitis and death in a 25-year-old woman who had an endoscopic cholangiogram out of state. Accordingly, we have tried to identify small stone disease that can be managed with intraoperative flouroscopic basket manipulation; we have succeeded in about 60% to 70% of cases. This technique is easy to do with instruments that you probably already have. Furthermore, flouroscopic cholangiograms obviate the need for the more expensive plastic cannulas.

We do obtain cholangiograms in 3% to 4% of patients with difficult anatomy but generally rely on careful dissection more than x-rays to keep us out of trouble. As a helpful pearl, if you are having difficulty sorting out the anatomy, use one of the cholangiogram catheters with a balloon to secure the catheter (do not use clips on what could be the common duct) until the anatomy is more clear.

I have three questions:

(1) What do you do if you want a preoperative cholangiogram but your endoscopic colleague is unsuccessful? Do you place a percutaneous wire through the liver into the duct? Do you do an open procedure, or do you proceed with intraoperative cholangiograms?

(2) We must always question costs. A normal cholangiogram must add $300 to $500 to the patient's bill. Do you know your hospital's charge for laparoscopic cholecystectomy? In a review of 50 patients, the patient charge from my hospital was less than $1900 with an overnight stay. I think that this is the lowest in the nation.

(3) How do you manage acute gallbladders with minor enzyme ele-

vation and a 5-mm duct? There is an increased incidence of common duct stones in this setting, but we are reluctant to obtain preoperative cholangiograms. We think intraoperative cholangiograms should be pursued more aggressively in this group. Thank you.

DR. KENNETH W. SHARP (Nashville, Tennessee): Thank you, Dr. Ochsner and Dr. Jones. Dr. Gadacz, my congratulations to you on a good paper that was well presented. I appreciate the opportunity to discuss this paper and appreciate your having given me the manuscript. Dr. Gadacz is truly one of the pioneers in the development of the technique of laparoscopic cholecystectomy. Its popularity is manifested in the sheer numbers of cholecystectomies performed. They accumulated 400 cholecystectomies in less than 2 years. During my 7 years as a resident at Hopkins, I think we did fewer than 200 cholecystectomies. Now that the technical aspects of the operation are becoming standard and its success rate has been shown to be very high and its morbidity rate acceptably low, we have several remaining questions about laparoscopic cholecystectomy. Number one, what is its overall safety? What are the short-term morbidity and mortality rates during the learning phase of the operation? Secondly, what is the long-term morbidity rate? And, thirdly, how do we answer some of the more difficult questions such as the management of common duct stones?

My specific questions for the authors are: One, with regard to short-term morbidity rate, I am concerned about the cystic duct stump leaks. In the manuscript, you report five patients who developed cystic duct stump leaks, and leaked bile into the peritoneal cavity, requiring endoscopic stint placement, percutaneous drainage, and, I believe, two open explorations. This is higher than any other report that I know of. How do you routinely handle the cystic duct stump? Do you use clips or preknotted ligatures? Do you make any decisions based on the size of the cystic duct? Does this complication represent a clip falling off? A clip not totally crossing the cystic duct? Or does it represent necrosis of the cystic duct stump due to the clip? We have had one leak in a similar patient that we believed was due to necrosis of the cystic duct stump from the clip. What is your long-term morbidity rate? I realize you followed the two patients with common bile duct injury very closely and continuously. But in the manuscript you mentioned that you only followed the other patients for one postoperative visit or 1 month. How do you know that there are not other late strictures developing? I would be particularly concerned about the patients with the biliary leaks, because I would think that cystic duct leak would lead to increased fibrosis and inflammation and possibly a late stricture. And then, thirdly, how do we manage common duct stones? We have agreed with the authors about the use of preoperative endoscopic retrograde cholangiography. We have performed preoperative endoscopic retrograde cholangiography in approximately 8% of our patients for fairly strict indications, pancreatitis, hyperamylasemia, elevated liver function tests, history of jaundice. We have had about half of those patients, very similar to your numbers, having the preoperative finding of common duct stones, which we have treated with endoscopic sphincterotomy without complication. How do you manage the patient in whom the endoscopist has attempted endoscopic retrograde cholangiopancreatography and is unable to do it? We have found that to be the case in an additional 3% to 4% of patients, patients on whom we would like to have a preoperative cholangiogram but the endoscopist is unable to cannulate the common duct. We generally have advocated routine intraoperative cholangiography and have attempted it in more than 90% of our cases. Our success rate is about 60%. We have only a 2% incidence of unsuspected common duct stones found in this fashion, and we have taken a very conservative approach here and have opened those patients for routine open cholecystectomy and common duct exploration.

Have you attempted transcystic common bile duct exploration? And how are you managing the patients who have no preoperative endoscopic retrograde cholangiopancreatography that you would like to have that information on? I would like to thank you for the privilege of reviewing the manuscript. I thought it was an excellent presentation.

DR. CHARLES UNDERWOOD (Marietta, Georgia): President Ochsner and Secretary Scott, Members, first I want to thank you for myself and my wife Ellie for membership in this organization. This is our first year as bona fide members, although we have been here as guests several times before. But we feel much more at home this year. We particularly feel honored that you ask an ordinary community surgeon who does not have a house staff behind him to join you. And to Tom Gadacz, I appreciate him asking me to discuss his paper. He probably was not aware that I have never been on this podium before, and for that lack of oversight, he deserves what he gets this morning.

This is, among others, a seminal and very important paper. This is true not only because it is good and frank and honest and admits the problems that he encountered, but it is true because before this Association in the coming years are going to hear a lot more papers similar to it. You are going to hear about colectomies and hysterectomies and common duct explorations and hernia repairs and Nissen fundoplications all being done today in some institutions, and you are going to see these papers proliferate before this Association in the years ahead.

I think you have heard this morning, from the standpoint of the appendix and the gallbladder, some very important seminal information. A very brief anecdote: We surgeons are slow to accept things. In the spring of 1988 I sat at a Wednesday morning surgery conference in Marietta and looked at a videotape that Dr. McKernan had brought over. It showed a laparoscopic cholecystectomy, said to be the first one done in this country. My fellow surgeons and I watched it as he dropped the gallbladder and it became lost and they searched for 30 or 40 minutes trying to find it, only to find it had disrupted and the stone had rolled into the pelvis and an hour or two later they found the stone. And we laughed at him and said "Take your tape on back across the street. You're not talking about anything that will ever work." And, of course, the rest of that story you know for yourself.

So much for history. In our hospital we have somewhat more than 800 cases. We always do them with a physician first assistant. We do 100% of them, at least try to, with operative cholangiography, and we are successful about 90% of the time. We use a Bovi electrocautery unit almost exclusively. We use reusable probes as a cost containment attempt. Our time is down to about an hour and 15 minutes. Complication-wise, we have had one postoperative bleeder — my own — that had to be reopened, two small bowel injuries, two bile loculations, one minor common duct injury, and we use the Hassan open technique exclusively.

The questions, Tom, that I would have for you relate very closely to those that have already been put to you. First, when you are dealing with a new procedure that is fraught now and even more so in the future with legal problems, litigation as to the experience of the surgeon, when you are dealing with a residency staff trying to learn a procedure that has a terribly difficult learning curve, why in the world would you advocate abandoning a procedure that in any way would add some degree of safety? Particularly in the courtroom, you would have some degree of certifying that you really did everything you could to avoid those injuries?

Secondly, realizing that in only 400 cases you have found the need to do two hepaticojejunostomies because of common duct injuries, why would you state in the paper, as you did, and I quote from it: "No attempt was made to dissect the cystic duct down to its junction with the common bile duct," and then later on in the paper the statement, "These results seem to support the role of careful dissection and visualization of ductal structures prior to division and suggest that intraoperative cholangiography is not necessary"? My question then is, do you really believe in careful dissection? And if so, why do you make the statement that you do not go down and visualize the common duct?

And, finally, would you tell us why you use the Bovi instead of a laser? Do you use reusable ports or disposable ports? Having produced one or two small bowel injuries, do you use the verres needle technique for introducing the pneumoperitoneum? And if you do, why so? And why do you not use the Hassan technique? Finally, I appreciate the courtesy of the floor and appreciate the Association giving me the privilege of responding to this paper.

DR. EUGENE SHIVELY (Campbellsville, Kentucky): Dr. Ochsner, Dr. Jones, Members and Guests, I think we are evolving into a new era of surgery, where there are superstars and then the ordinary surgeon out in the community. And I think the group from Johns Hopkins and Randy Voyles, who was a junior resident of mine, are superstars. But I do not think all of us are in this category. Most of my friends in tertiary medical centers are reporting a very high incidence of common duct injuries, two and three times more than they were seeing before the advent of laparoscopic cholecystectomy. In personal communication with Dr. Eddie Redick of Nashville, who was one of the pioneers of this operation in the United States, he states that in all the videotapes that he has reviewed where there was a common duct injury, no cholangiogram was performed. I personally know of two cases where the entire common duct was removed through the laparoscope. There are several studies that demonstrate that routine cholangiography not only detects occult common duct stones, but also increase the safety of open cholecystectomy. Dissection in the triangle of Calot is dangerous, and we do not have the opportunity to take the gallbladder down in a retrograde manner as we do in open cholecystectomy. The most difficult part of laparoscopic cholecystectomy is the cholangiogram, and in my opinion it is important to have extensive experience in this.

My first question is, what has been the experience at Johns Hopkins in referrals from outside community hospitals with injured common ducts secondary to laparoscopic cholecystectomy?

Endoscopic retrograde cholangiopancreatography also fits into the category of a very high-tech procedure where there are only scattered superstars who are very good at this. Most community surgeons do not have endoscopists who are experts at sphincterotomy.

My second and last question is, do you have reservations about doing sphincterotomies in young patients, and what do you think the long-term consequence of this will be? I would like to thank the Association for membership. It is certainly one of the highest honors of my professional career. Thank you.

DR. T. R. GADACZ (Closing discussion): I greatly appreciate the comments of the reviewers and would like to answer the questions in groups rather than individually. Our approach to common stones is determined by the expertise in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy. We rely on this approach preoperatively or if small stones are discovered postoperatively. Several patients with common duct stones that we saw early in our experience were not included in this series because we performed open cholecystectomy and common duct exploration. There remains a role for open cholecystectomy and common duct exploration in patients with multiple and large common duct stones.

Our current approach for suspected common duct stones is in transition. For large or numerous common duct stones, a standard open cholecystectomy and duct exploration is favored. For small or few stones, laparoscopic extraction is attempted. Recently at the Medical College of Georgia, a patient with multiple common duct stones had successful extraction with a balloon and basket. The choledocoscope was used through the laparoscope to extract stones and confirm that her common bile duct was free of stones. A closing cholangiogram showed no stones. Techniques to explore the common duct through the laparoscope are improving.

Regarding some of the questions of short-term and long-term morbidity rates, we had five cystic duct leaks. Two of these were confirmed. Two of them occurred very early during our experience when we were using a reusable clip applier. There were problems with this clip applier, which have been remedied. The clip scissored in both patients, resulting in early dislodgement and a cystic duct leak. The leak was confirmed by a technetium study. She was re-explored immediately, and a suture was used to secure her cystic duct. The other cystic duct leak had the diagnosis made by endoscopic retrograde cholangiogram. An endoscopic stent was placed but was not successful, and he required reoperation and tying of the cystic duct. The other three patients had collections on ultrasound in the subhepatic area. One of these was successfully drained percutaneously. A bile duct leak could not be demonstrated. Whether this was a cystic duct leak or a leak from the bed of the gallbladder and accessory duct is not known. The two other patients did not have a demonstrable leak and resolved without further treatment.

The incidence of common duct injuries varies between series, and the long-term complications are not known. In our two patients with common duct injuries, there have been no complications after reconstruction. Both injuries were recognized immediately and repaired. We have been referred patients with common duct injuries that were not recognized at the time of laparoscopic cholecystectomy. They required a hepaticojejunostomy and seem to be doing well. Some of the reports with no common duct injuries may reflect a lack of early recognition.

There are several technical aspects to avoid complications. It is important to ensure that the clips are secure and to inspect the clips after application. We do not use cautery to divide the cystic duct. Cautery should be used to dissect the peritoneum away from the gallbladder and the gallbladder from the hepatic bed.

We dissect the cystic duct from the neck of the gallbladder toward the common duct. This is a crucial part of the procedure. A 30° angled endoscope is used and provides good visualization of the cystic duct. The entire cystic duct should not be dissected, but it is important to identify the neck of the gallbladder and the cystic duct. Both of our injuries occurred during dissection of the cystic duct.

Our preference in instruments is the re-usables. They are the most economic. We had one small bowel injury that could not have been avoided. It occurred in a patient with no previous operation but a loop of jejunum adhered to the umbilical area.

We do not support the use of routine preoperative endoscopic cholangiography or sphincterotomy in patients undergoing laparoscopic cholecystectomy. Some of these patients are very young, and there may be long-term sequelae from these procedures. By taking a good history and doing the appropriate preoperative laboratory studies, most patients with common duct stones can be identified. And then, where appropriate, the study can be done. In young patients with a few small common duct stones, laparoscopic extraction may be better than an endoscopic sphincterotomy. There remains a role for open cholecystectomy and common duct exploration.

Although we do not oppose routine intraoperative cholangiography, we wish to caution surgeons that this does not prevent common duct injuries.

I wish to thank the Association for the opportunity to present this paper and the discussants for their comments and questions.

Formal Hepatic Resection of Colorectal Liver Metastases

Ploidy and Prognosis

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Fifty consecutive patients who underwent 52 formal hepatic resections (excluding isolated wedge resections) for metastatic colorectal cancer were analyzed to determine whether DNA content was of prognostic significance. The Dukes' stages of the colorectal primaries were: A (10%), B (20%), C (40%), D (28%), and unknown in 2%. Four patients whose liver metastases were discovered at the time of resection of the primary bowel cancer underwent concomitant liver resection, and the remaining patients underwent delayed resections. The hepatic resections performed were right lobectomy (50%), extended right lobectomy (19%), left lobectomy (13%), left lateral segmentectomy (6%), left lobectomy and right wedge (6%), extended left lobectomy (4%), and right lobectomy and left wedge (2%). The overall morbidity rate was 29%. The in-hospital mortality rate was 9%. As of November 1991, 36 patients have recurred. The 5-year actuarial survival was 28%. Flow cytometry could be performed on 37 archival specimens, 15 of which were found to be diploid whereas 22 were aneuploid. All metastases from Dukes A colorectal primaries demonstrated a diploid DNA content. In addition, there was no difference in actuarial survival between diploid and aneuploid tumors. These data suggest that in selected patients, formal hepatic resection of colorectal liver metastases can be performed with an acceptable morbidity rate, mortality rate, and survival, but ploidy of the resected tumor is not of prognostic significance.

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THE LIVER IS a frequent and often the only site of metastases from colorectal cancer. As many as 10% of patients with colorectal cancer present with concomitant liver metastases at the time of detection of their primary tumor and, in many patients who undergo presumed curative resection of their colorectal primary, the liver is a major site of recurrence. In the last decade, the number of resections of colorectal liver metastases has increased dramatically, and yet there remains no consensus among surgeons regarding the appropriate indications for resection.

Evidence is accumulating that flow cytometric analysis of DNA content has prognostic significance in many malignancies.[1] Relatively few studies have examined the prognostic significance of ploidy in colorectal liver metastases.[2,3] Ploidy may provide a reliable, objective indicator of tumor biology that may identify patients with neoplasms who are less likely to benefit from surgical intervention. In addition, now that chemotherapy has been shown to have a modest effect on the natural history of colorectal cancer,[4] future protocols of hepatic resection will undoubtedly include chemotherapy arms. Properly designed clinical trials require knowledge about important prognostic variables. Therefore, we sought to review our results with formal hepatic resection of colorectal liver metastases and to determine if DNA content of the resected metastases was of prognostic significance.

Materials and Methods

Patients

The records of all patients who underwent formal hepatic resection of colorectal liver metastases at the Medical College of Virginia from January 1980 to January 1991 were reviewed. Isolated wedge resections were excluded from analysis. There were a total of 50 patients who underwent 52 formal resections with curative intent. The female:male ratio was 1.2:1, and the ages ranged from 37 to 81 years, with a median of 56 years. The Dukes' stages of the colorectal primaries were: A in 5 patients, B in 10

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patients, C in 20 patients, D in 14 patients, and unknown in 1 patient. Hepatic recurrence was detected by a rising carcinoembryonic antigen level in 30 patients, whereas four patients were symptomatic, prompting computed tomography (CT scan). One patient presented with jaundice, whereas in another patient hepatic recurrence was detected at the time of laparotomy for a small bowel obstruction. Preoperative evaluation consisted of physical examination and standard laboratory and radiologic assessment. Hepatic imaging consisted primarily of contrast-enhanced CT scan and, more recently, dynamic CT scan. If the CT scan suggested the need for a major hepatic resection (*i.e.*, lobectomy or extended lobectomy), hepatic angiography was performed to delineate hepatic arterial anatomy. In the absence of severe comorbid disease, obvious extrahepatic disease, or more than three hepatic metastases, laparotomy was advised. Intraoperative sonography was routinely performed at the time of exploration to identify lesions not seen on CT scan as well as to demonstrate hepatic venous anatomy. The extent of hepatic resection performed appears in Table 1. Of the 14 patients whose liver metastases were discovered at the time of resection of their primary bowel cancer (*i.e.*, synchronous metastases), four underwent concomitant liver resection. Two patients with Dukes stage D disease at presentation had wedge resections of liver metastases performed concomitant with resection of the colorectal primary at an outside institution. They subsequently developed hepatic recurrence, prompting referral for formal hepatic resection. In the remaining eight patients with synchronous metastases, formal hepatic resection was delayed 1 to 2 months after their bowel surgery. In those patients presenting with metachronous liver metastases, the interval from bowel surgery to liver resection ranged from 2 to 88 months, with a median of 20 months. Patient follow-up after hepatic resection was determined by the individual surgeon. Only two patients received adjuvant chemotherapy after hepatic resection.

Preparation of Single-cell Suspension

All resected liver specimens were previously fixed in formalin. Approximately four to five 50-μm sections were prepared from the paraffin-embedded blocks (Before preparation, a section of each block was examined pathologically to verify the presence of tumor.). The tissue then was deparaffinized in xylene followed by progressive rehydration in ethanol at decreasing concentrations. The tissue was then minced into small pieces, resuspended in 0.5% pepsin solution, and incubated for 2 hours at 37 C. After centrifugation at 1200 rpm for 5 minutes, the pellet was resuspended in RPMI 1640 culture media (Whittaker Labs, Walkersville, MD), filtered through 40-μm nylon mesh to remove clumps, and counted to assure recovery of $>1.0 \times 10^5$ total cells. The cells were again centrifuged, washed, and stored overnight in RPMI-1640 at 2 to 8 C.

TABLE 1. *Extent of Hepatic Resection*

Hepatic Resection	No. of Patients
Right lobectomy	26 (50%)
Extended right lobectomy	10 (19%)
Left lobectomy	7 (13%)
Left lateral segmentectomy	3 (6%)
Left lobectomy and right wedge	3 (6%)
Extended left lobectomy	2 (4%)
Right lobectomy and left wedge	1 (2%)

Cell Staining and DNA Analysis

After storage, the cells were first centrifuged at 1200 rpm for 5 minutes, then the pellet was resuspended in phosphate-buffered saline (1.0×10^6 cells per 0.4 mL) and incubated in a 0.003% trypsin solution for 10 minutes. This was followed by the addition of a mixture of 2.5% trypsin inhibitor and 0.5% ribonuclease A and incubation for an additional 10 minutes. A solution of 2.5% propidium iodide and 5.8% spermine tetrachloride (Sigma Chemical Co., St. Louis, MO) then was added directly to the cells on ice in light-free conditions. After 10 minutes, the cells were centrifuged at 1200 rpm for 5 minutes and resuspended in 1 mL RPMI. Cellular DNA was measured using a flow cytometer (FACSCAN, Becton Dickinson, Mountainveiw, CA). Data were analyzed using RFIT DNA software (Becton Dickinson). When possible, flow cytometric analysis also was run on normal liver as a control.

Definitions

Flow cytometric analysis of specimens was performed by a single pathologist who was unaware of the clinical outcome of the patients. Tumors were considered diploid if the DNA histogram displayed a single G_0/G_1 peak, whereas aneuploid tumors demonstrated more than one G_0/G_1 peak.

Statistical Analysis

Statistical analysis was done using the SAS statistical software package (SAS Institution, Cary, NC). Survival curves were generated using the Kaplan-Meier method.[5] Statistical significance between survival curves was determined by the Wilcoxon log-rank test.[6]

Results

Morbidity and Mortality Rates

There were 16 complications, for a 29% morbidity rate. Not unexpectedly, the most frequent complication was a collection of bile (biloma). The in-hospital mortality rate was 9%. The complications and causes of death appear in Table 2. The median estimated blood loss was 3000 mL (range, 700 to 15,000 mL) and the median hospital stay was 16 days (range, 7 to 38 days). Patients who underwent liver resections concomitant with removal of the primary tumor and those in whom the estimated blood loss exceeded 3 L tended to have more complications, although this did not reach statistical significance ($p = 0.051$). There was no relationship between age or extent of hepatic resection and frequency of complications.

Pathology of Hepatic Metastases

The pathologic characteristics of the resected specimens appears in Table 3. Sixty-two per cent of patients had a single metastasis after pathologic examination of the resected specimen. Grossly, no patient had more than three metastases, but three resected specimens did exhibit tumor satellites surrounding a single metastasis. The size of lesions ranged from 0.5 to 15.0 cm, with a median of 6.2 cm. The pathologic margins were free of tumor in 81% of patients, microscopically involved in 17%, and unknown in 2%.

Pattern and Treatment of Recurrence

As of November 1991, 36 patients have recurred. Recurrence was determined by clinical, radiologic, and pathologic means. The locations of recurrences appear in Table 4. Most of those patients in whom the margins of resection were microscopically involved had recurrences in the liver. Of those 15 patients in whom the liver alone was the site of first recurrence, 10 were re-explored and five were reresected. Table 5 illustrates the characteristics of the reresected patients. One patient in whom the brain was the sole site of first recurrence, and another patient in whom the lung was the sole site of first recurrence, were treated surgically. One patient who recurred in the liver, but was unresectable at re-exploration, was treated with cryotherapy, whereas another was treated with combined interstitial and external beam radiotherapy and chemotherapy. An additional 10 patients who had recurrences were treated with chemotherapy.

TABLE 2. *Morbidity and Mortality Rates*

Complication	No. of Patients: Nonfatal	No. of Patients: Fatal
Biloma/abscess	8	—
Pleural effusion	4	—
Pneumothorax	1	—
Deep vein thrombosis	1	—
Splenectomy	1	—
Coagulopathy	1	1
Liver failure	—	2
Myocardial infarction	—	1
Necrotizing fasciitis	—	1
Total	16/55 (29%)	5/55 (9%)

TABLE 3. *Pathologic Characteristics*

Characteristic	No. of Patients
Microscopic margins	
Negative	42 (81%)
Positive	9 (17%)
Unknown	1 (2%)
No. of metastases	
Solitary	32 (62%)
Two	12 (23%)
Three	8 (15%)
Size of metastases	
<6 cm	27 (52%)
>6 cm	25 (48%)
Distribution of metastases	
Unilobar	46 (88%)
Bilobar	6 (12%)

Survival

As of November 1991, 36 patients have died: five were operative deaths and one patient died of pneumonia 3 months after operation with no evidence of disease. The remaining 30 patients died of disease. Fourteen patients are alive: five with disease, and the remaining nine have no evidence of disease. The median follow-up of those patients alive without any evidence of disease is 41.5 months. The actuarial survival curve appears in Figure 1.

Ploidy of Resected Hepatic Metastases

Paraffin-embedded blocks were recovered for 37 patients. DNA histograms produced from tissue fixed before 1983 were excluded secondary to fixative-induced artifact. DNA histograms representative of diploid and aneuploid specimens appear in Figure 2. The median coefficient of variance of all DNA histograms was 4.3 (range, 0.5 to 9.3). The effect of DNA content on actuarial survival appears in Figure 3.

Discussion

The natural history of colorectal liver metastases is not one of uniform demise within 6 months, but one of vary-

TABLE 4. *Pattern of Recurrence*

Site	No. of Patients
Liver	15
Lung	7
Brain	2
Multiple sites (including liver)	7
Multiple sites (excluding liver)	5
Total	36

TABLE 5. *Hepatic Reresections*

	First Resection		Second Resection	
Patient	Type of Resection	Disease-free Interval	Type of Resection	Status
1	Left lateral segment	19 mo	Right lobectomy	DOD 26 mo
2	Left lateral segment	11 mo	Left lobectomy	DOD 22 mo (liver negative)
3	Extended right lobectomy	26 mo	Wedge left lobe	DOD 34 mo (liver negative)
4	Left lobectomy	13 mo	Wedge right lobe	NED 18 mo
5	Extended left lobectomy	31 mo	Wedge right lobe	NED 46 mo

DOD, dead of disease; NED, no evidence of disease.

ing survival depending primarily on tumor biology and extent of liver involvement. Better knowledge of liver anatomy as well as improved surgical techniques and perioperative care have resulted in a marked increase in the number of hepatic resections performed for colorectal liver metastases. Many argue that the results attributed to surgery merely reflect tumor biology rather than surgical success.[7] Certainly those patients who undergo resection represent a select group. Our experience echoes the fact that preoperative staging is notoriously inaccurate. Imaging studies tend to grossly underestimate the number of liver metastases and are even less sensitive at detecting intra-abdominal extrahepatic disease.[8] More sophisticated and sensitive imaging studies are becoming available, but their specificity is not yet sufficient to deny patients laparotomy.[9] Exploration allows more accurate staging of the extent of disease. Therefore, survival comparisons made between operative and nonoperative groups are inappropriate. In addition, those patients considered as candidates for exploration inherently have a better prognosis simply because of less comorbid disease. Undoubtedly, surgical selection plays a role in ultimate outcome, but in the absence of any other effective therapy or a controlled randomized trial, resection remains the treatment of choice for selected patients with hepatic colorectal metastases.

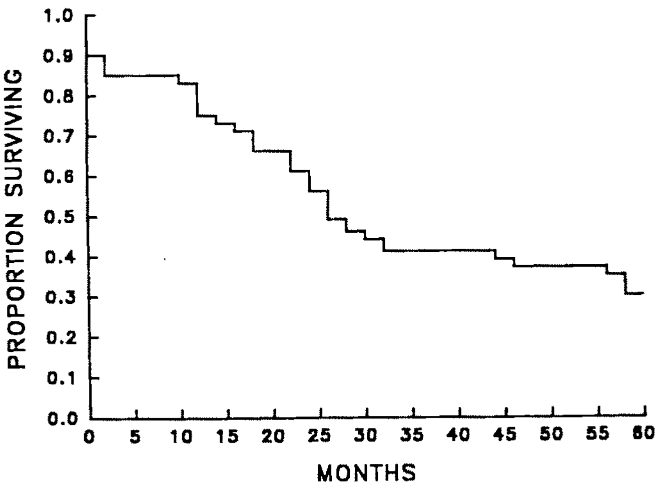

FIG. 1. Actuarial survival of patients undergoing formal hepatic resection of colorectal liver metastases.

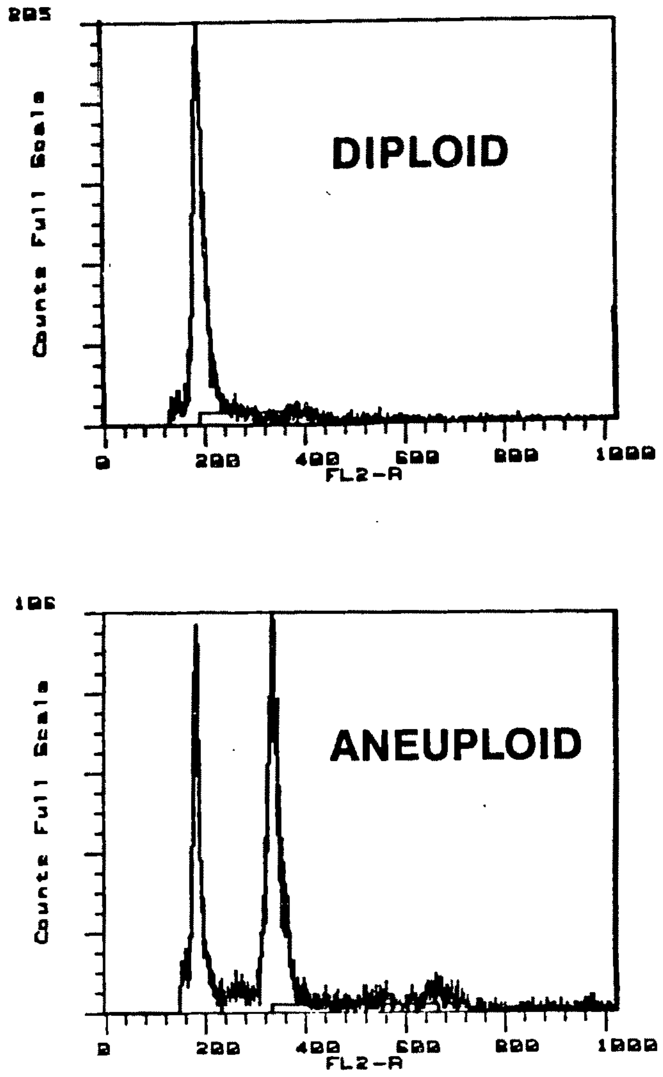

FIG. 2. Representative DNA histograms of resected metastases.

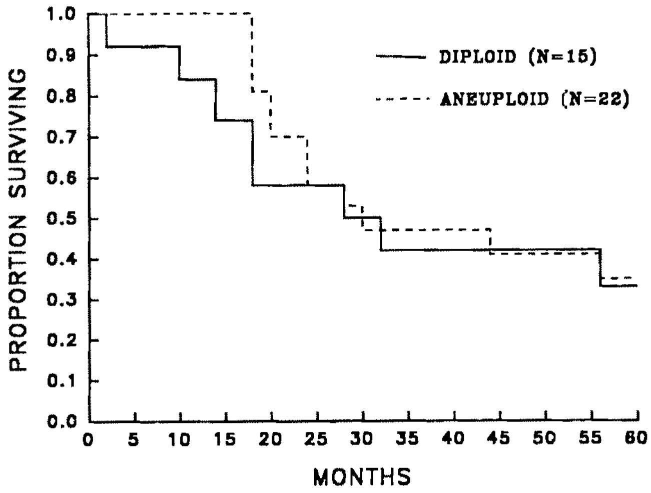

FIG. 3. Actuarial survival of patients undergoing formal hepatic resection of colorectal liver metastases: diploid *versus* aneuploid.

The selection criteria for resection of hepatic metastases from colorectal carcinoma remain controversial. At one extreme, some advocate a "swiss cheese" approach, resecting up to 13 separate liver metastases, and claim improved survival.[10] Others prefer to "watch and wait," allowing those who may not benefit from resection to declare themselves.[11] This biologic selection process may improve survival statistics, but also may deny some patients a potentially curative resection. Many of the generally accepted criteria for resection have been generated from pooled data.[12] Typically, we favor exploration in patients without evidence of extrahepatic disease and in whom there are less than four liver metastases documented by preoperative imaging. Occasionally a more aggressive surgical approach is justified. For example, a patient with solitary liver and lung metastases may benefit from staged resections.

The operative technique of hepatic resection varies widely. Recently a variety of sophisticated devices have been brought into the operating room to aid the surgeon performing hepatic resection.[13] No method has been proven superior, and we prefer finger fracture with meticulous hemostasis. One technique we have found useful is intraoperative ultrasound. Previously we have reported that intraoperative ultrasound was the most sensitive indicator of the number of lesions present in the liver and affected operative decision making in 49% of liver resections for both primary and metastatic tumors.[14] The amount of liver to resect is also controversial. Some advocate wedge resection, others formal hepatic resection, and still others favor segmentectomy.[15] Often it is safer to perform a formal resection rather then a large wedge resection, but the paramount principle is to remove the lesion with a adequate margin.

Although multi-institutional studies are valuable, it is impossible to standardize surgery and therefore it is imperative for single institutions to periodically review their results. Our morbidity rate of 29% is comparable to that in published reports,[12] and when one considers that this study excluded isolated wedge resections, a 9% mortality rate is not unreasonable. In addition, most of the in-hospital deaths were in the first few years of the study, and there have been no operative deaths in the last 4 years.

There is evidence to suggest that patients with synchronous metastases who undergo liver resection concomitant with resection of the colorectal primary have impaired survival compared with those who undergo delayed resection.[16] Although it is difficult to sort out selection factors with respect to survival in these patients, our data at least suggest an increased morbidity rate with concomitant formal hepatic resection. Most of these patients were in the first few years of the study. We now favor a policy of concomitant wedge resection or left lateral segmentectomy, but delay formal hepatic resection until the patient has recovered from his or her bowel surgery. The finding that intraoperative blood loss of more than 3 L correlates with postoperative complications has been reported by others[17] and may be related simply to the extent of resection. This assumes greater importance if one considers other reports of a detrimental effect of perioperative transfusion,[18] and more recently hypotension, on ultimate survival.[19]

The patterns of recurrence in this study are similar to those reported by others.[20] Some of these recurrences represent occult disease not detectable at the time of liver resection. The liver alone was a site of recurrence in 42% of cases. Liver recurrence either alone or as a part of disseminated disease was more common when the pathologic margins of the hepatic resection were positive and in the presence of bilobar metastases. Those patients with recurrence confined to the liver and believed to be suitable candidates for reresection were reexplored. Five of these patients were reresected, and two patients are alive without evidence of disease 18 and 48 months after the hepatic reresection. Although these numbers are small, combined with other reports[21,22] they suggest that reresection of colorectal liver metastases is also beneficial in selected patients. The frequency of isolated liver recurrences raises the question whether regional adjuvant therapy might have any impact. Although it suffers from small numbers, one prospective randomized study recently reported an increased time to treatment failure in patients with solitary metastases that were resected and received intra-arterial FUdR after operation. Furthermore, none of those patients had recurrences in the liver.[23] This, together with the data presented here in which the lung and multiple sites (excluding liver) were frequent sites of recurrence, emphasize the need for effective systemic adjuvant therapy. The 5-year survival rate of 28% is similar to that in other published results. Some data suggest a plateau in the survival curve at 5 years,[12] whereas others argue that these patients are never cured in that their survival curves never approach those of age-matched controls.[24] Although our data appeared to plateau, we did have a few late recurrences, emphasizing the need for long-term follow-up.

Several studies have found flow cytometric analysis of tumor DNA ploidy to be of prognostic significance in a number of malignancies.[25] Kokal et al.[26] found ploidy to be the single most important variable in predicting both recurrence and death from disease in primary colorectal cancer. Others argue that DNA content provides little prognostic information over and above routine clinical and pathologic parameters.[27] Although there is good correlation between fresh and archival samples with respect to ploidy,[28] many studies fail to retrieve material on all patients, and therefore the data may not be representative of the entire population. Small sample size, limited follow-up, and methodologic variation between institutions represent additional potential sources of error.

In spite of these shortcomings, ploidy may offer an objective measurement of tumor biology. There are few data concerning the prognostic significance of DNA content of hepatic metastases from colorectal cancer. In a study of 65 hepatic metastases from large bowel cancer, Yamaguchi et al.[3] found DNA ploidy patterns to be a useful indicator of prognosis when subjected to multivariate analysis. Kokal et al.,[2] however, found that DNA content of 53 liver metastases from colorectal cancer bore no relationship to survival or response to therapy. Ten per cent of patients in this study had Dukes A colorectal primary tumors, and, in spite of this favorable pathology, developed hepatic metastases. All of these colorectal primaries were diploid by flow cytometry. This small number together with a failure to analyze a similar cohort of patients with Dukes A lesions who failed to develop metastases make any valid statistical analysis impossible.

When we examined the relationship between ploidy and disease-free and overall survival, our data are consistent with those of Kokal et al.[2] There was no statistically significant difference in actuarial survival with respect to DNA content of the resected hepatic colorectal metastases. Although we were unable to accurately analyze the DNA histograms of specimens fixed before 1983, overall survival of these patients was representative of the original cohort. In addition, therapy of treatment failures (*i.e.*, those that recurred after hepatic resection) was similar between diploid and aneuploid groups. Although this study suffers from small numbers, it suggests that once distant metastases are present, ploidy has no effect on survival. Other studies support the contention that in more advanced stages of disease tumor ploidy loses any prognostic significance.[29]

Our experience suggests that in selected patients, formal hepatic resection of colorectal liver metastases can be performed with acceptable morbidity, mortality, and survival rates, but DNA content of the resected tumor is not of prognostic with respect to survival. Unfortunately, patterns of recurrence stress the fact that surgery remains a local therapeutic modality, and more effective systemic therapy is desperately needed.

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DISCUSSION

DR. R. SCOTT JONES (Charlottesville, Virginia): I want to compliment Dr. Parker and his colleagues for an excellent piece of work. This obviously is a fairly large series of patients accumulated over a short period and treated quite expertly. And I think that Dr. Parker should be congratulated. I think much of the information that he presented would certainly support clearly the information that has accumulated from a number of institutions and is currently in the literature. And I think the new thing that he looks at that really deserves comment is the issue of what is the role of looking at DNA as a prognostic indicator. And the data that he showed us would suggest it is not particularly helpful, but I would like to suggest that there are some different ways of looking at this. Particularly, with the data that Dr. Parker has, he could look at the nature of the primary tumors. He has the opportunity to look at the tumors that were metastatic in the liver, which I think was information he showed us today. And he also has an opportunity to look at recurrent tumors after liver metastases.

Now the reason I make that point is that it is theoretically possible that that information may change from one of those populations to the other. And it would be interesting to know, and you have the resources available to take a look at that. I think it would be especially interesting to know what the tumors looked like in those patients who were re-resected. It might be interesting that those patients constitute a special subpopulation.

I wanted to make one other point about flow cytometry and liver tumors. It was just a coincidence I happened to have on my desk some information when I talked to Dr. Parker about his work. There is a publication from Japan by Fujimoto. They studied a large number, 203 patients, who had hepatocellular carcinoma, in which all were resected. They did the same kind of study on these hepatocellular carcinomas. And they found that the flow cytometry was a significant prognostic indicator in that population of patients. I think it is interesting to draw the contrast between that series of patients who had primary hepatocellular carcinomas and in whom DNA content was significantly predictive of survival and Dr. Parker's population of patients of metastatic tumors in whom it was not. So I think that there is probably some room for further investigation in this issue of the biologic nature of the material in terms of prognosis.

In any event, I want to support Dr. Parker and his colleagues in their work. I think they are really doing excellent work in this field, and it was a pleasure to hear your presentation, Dr. Parker, and also to read your manuscript. Thank you very much.

DR. HAROLD J. WANEBO (Providence, Rhode Island): President Ochsner, Dr. Jones, I also want to compliment Dr. Parker and his group for both an excellent presentation and a nice review and their effort to look at ploidy. It was interesting that he showed that some patients with Dukes' A cancer can metastasize. I think we are all aware of that, but sometimes we forget that point. I think your 5-year survival rate basically parallels what has been reported in the literature. And also, I think you point out that there is a failure rate of 70%, and this is an area that we have to address. I have some questions. First of all, George, in your examination of the margin, you had 80% clear margins, but you also had about 20% positive margins. Do you take any steps to avoid getting a positive margin? I have been dismayed myself to find that after resection when I give it to the pathologist, he will frequently say, "Oh, this margin is close." And I will go back and redo it. So now I ink all our specimens, and I just wondered is this of value.

You mentioned that there was not a survival difference in the group that had positive margins, but I just wondered if you look at that more carefully whether or not there is some subtle change. I think Kevin Hughes has shown that the ones who did the best in their natural history survival registry were the ones that did have clear margins.

The second question I would ask is, are there some negative selection factors? Are there some patients on whom we actually should not operate? For example, the patient who has a short free interval whose primary tumor was an aggressive Dukes C. I am personally always concerned about that group and would wonder if it is of value to try to resect those patients. Thirdly, there is a problem sometimes with blood loss in these patients. Is there value in using something like the cell saver? Again, I want to thank the Association for the privilege of the floor and the opportunity to hear this very nice paper.

DR. LESTER WILLIAMS (Nashville, Tennessee): Dr. Ochsner, Dr. Jones, I tried to decline the request to discuss this paper on the basis that I was a reluctant supporter of the general concept. Dr. Parker convinced me that I should make that point even though it would be less than supportive. Thus, I have seen the manuscript and I did agree to discuss it.

Before going to Nashville, I was exposed to the philosophy of Blake Cady, Bill McDermott and Bill Silen and that is the basis for saying I might be less than supportive. Their philosophy was that the patients who fulfill the usually accepted criteria to have the liver resected usually have a small bulk of tumor confined to the liver. By that observation alone in almost all cases, they have a biologically favorable tumor. And the issue for us is not that the patient lived longer than appropriate controls, but lived longer than the "expected death within months," derived from historic controls. And so they have been suggesting that the best criterion for a biologically favorable tumor was the fact that it could be resected. In fact, in this manuscript that is true for most of these patients, as it is for most other reports. We now know that ploidy does not help us much. This question is, can we pick out favorable patients? And if we cannot, should we begin to look at adjuvant therapy and accept that the patient who becomes a candidate for this kind of surgery is by definition—although we do not understand why—biologically different than most. And as such, are there routine adjuvant ways that we should be treating these patients? Thank you for the opportunity to discuss it.

DR. D. SCOTT LIND (Closing discussion): Thank you, Dr. Ochsner and Dr. Jones. First, I want to thank Dr. Parker and the Society for the opportunity to attend the meeting and the privilege to close on this paper. I also want to thank the discussants for their valuable questions.

First, Dr. Jones, you mentioned that study from Japan. I think there they were looking at primary hepatocellular carcinoma. Here we are looking at metastatic disease. And I think one of the reasons that we may not have found that ploidy was prognostic was that the disease has advanced to the point where ploidy is no longer a prognostic factor. And there is support in the literature for that. Dr. Kokal in the *Archives of Surgery,* 1986, showed that ploidy was an important prognosticator in primary colorectal cancer but lost its effect once the disease had metastasized.

The other question about looking at the patients that we re-resected, looking at their ploidy, I think is a good one. We have not done this; the numbers are small. But I think it would be valuable to pursue that in the future. Your other point about comparing the ploidy of the primary with that of the resected metastasis, we have not done that. That also would be a good idea. That has been done in the past, and ploidy does tend to remain constant with the progression of disease.

Dr. Wanebo, your question about the Dukes A patients: as Dr. Parker mentioned, we were surprised that we had so many. We did look at the ploidy of these resected primaries and found that although there were only five, they were all diploid — clearly too small a group to make any significant deduction about that. As you mentioned, we did have a 19% rate of microscopically positive margins. We do not routinely rely on intraoperative margins sending it over to pathology. I think one reason why some of these we did not see recur was that maybe we picked up their distant metastases, and they died before detection of their local recurrence. As far as the disease-free interval goes, our Dukes C patients did have impaired overall survival, but I do not think it was low enough to deny them potentially curative resection. We do use the cell saver when we feel it is required. Our preoperative imaging studies have been notoriously inaccurate and, therefore, many patients that are explored, perhaps about 50%, are not resected, so we do not line up the patients initially. We wait to decide whether or not it is a go and then use the cell saver and appropriate monitoring devices.

Dr. Williams, regarding your questions, clearly, I agree with you, this is a select group, and there are a number of selection factors that work here. There never will be a randomized prospective study, but I still think in the absence of any other effective therapy that this is the therapy of choice. There are no good selection criteria. Some argue that you can resect from one to 13 metastases in a Swiss cheese approach. Others adopt a watch-and-wait philosophy; however, some of those patients may be denied a potentially curative resection. And we kind of adopt a compromise policy, and patients that have no severe comorbid disease and have no more than three metastases on a preoperative imaging study or extrahepatic metastases are the patients that we think should undergo exploration.

I would like to show one additional slide, if I could. We also looked at S-phase and I will remind you that these were performed on paraffin-embedded archival specimens, but we found no difference in survival with respect to S-phase. Our median S-phase was 28, which is very high, and there was no difference. And I think, once again, this just echoes the fact that we are dealing with metastatic disease. And at this point the ploidy or S-phase fraction, which is indicative of the prolific activity of the tumor, loses its prognostic significance. I would like to thank the Society for the privilege of the floor.

Composite Resection of Posterior Pelvic Malignancy

HAROLD J. WANEBO, M.D., R. JAMES KONESS, M.D., PETER S. TURK, M.D., and STEVEN I. COHEN, M.D.

Advanced pelvic cancer is a formidable challenge to surgical resection. These tumors commonly invade the bony pelvis, may involve other viscera, and usually have been irradiated previously. The authors are presenting experience with 76 patients who had composite resection of posterior or lateral pelvic malignancy. Fifty-eight patients had secondary cancers involving the musculoskeletal pelvis. This included 47 patients with advanced carcinoma of the rectum (41 curative, 6 palliative), 10 epidermoid cancers of the anorectum (8) or cervix (2), and 1 bladder cancer. Among the 18 patients with primary pelvic tumors were three patients with chordomas, six with bone tumors (osteosarcoma chondrosarcoma, grade III giant cell tumor), and nine with soft tissue tumors. All required major resection of the sacrum or pelvic side walls, and one half had an additional exenterative procedure. The overall mortality rate was 7.9%. Long-term estimated survival was 24% in patients having curative resection of recurrent rectal cancer, and 22.5% in 10 patients with advanced epidermoid cancer. Fifty per cent of patients with primary bone or soft tissue tumors survived from 13 to 88 months. Most patients had reasonable return of function, and were able to return to work or resume their normal previous lifestyle.

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EXTENSIVE TUMORS OF the musculoskeletal pelvis are formidable challenges to the surgeon. Depending on location and tumor histology, there are complex biologic considerations, as well as inherent technical difficulties facing the extirpative surgeon, and short- and long-term risks to the patient.[1] The major issue is oncologic control, which requires complete resection of all tumor complemented by radiation therapy or chemotherapy where appropriate.[2] Of equal importance to surgical resectability and patient tolerance of the procedure is the potential for function preservation,[3-7] and the needs for reconstruction and rehabilitation, and perhaps, long-term adjuvant therapy.[8] The necessity of a multidisciplinary surgical and oncologic approach is obvious.

The nature and location of the tumor largely determine the options for resection. Primary tumors of the lateral pelvis (ileum, ischium) may be resected using a limb-conserving approach (internal hemipelvectomy),[3-7] whereas secondary tumors in these areas are often more invasive into surrounding soft tissues, and are less amenable to conservative resection, requiring a full or modified hemipelvectomy.[1-3] Primary tumors of the posterior pelvis (sacrum) are usually amenable to sacral resection with preservation of rectum.[9-13] After resection of these lesions, issues of urogenital and anorectal denervation and possible lower extremity weakness may require aggressive efforts at physical therapy and rehabilitation.[9,12] Secondary tumors in this area are more extensive, requiring composite resection of viscera, soft tissue, and bone. Commonly, an exenterative procedure is done in conjunction with the complete soft tissue and bone resection.[12-18] In most cases, neuromuscular function can be retained, with extremely aggressive resections or amputations rarely required.[15]

This paper emphasizes the surgical approaches and results in treating a group of patients with a variety of primary and secondary tumors involving viscera and musculoskeletal elements of the pelvis.

Materials and Methods

Preoperative Evaluation

Clinical examination included careful assessment of neuromuscular function of lower extremities and any preexisting deficits related to the tumor. A rectal examination (if feasible) and vaginal examination helped to assess tumor extent, lateral wall fixation, and possible involvement

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of anterior pelvic viscera (bladder). Essential radiologic studies included computed tomography of pelvis and abdomen, chest film, plain films of lumbosacral bones, bone scan, and in selected patients, a magnetic resonance imaging scan. The sagittal view of magnetic resonance imaging was useful to indicate the extent and level of sacral involvement. Arteriograms were done only in patients with extensive tumors. A computed tomography–directed fine needle aspiration cytology was used to confirm presence of advanced rectal cancer or epidermoid cancer. Although fine needle aspiration was less accurate with primary tumors, it was useful in many patients when combined with radiologic findings. In selected cases of primary tumors of the sacrum, an open biopsy was required.

Preoperative Planning

In addition to surgical planning, preoperative therapy was considered in all patients. Patients with large bulky primary sarcomas were considered for preoperative therapy with radiation or chemotherapy. In other primary tumors, such as chordomas, postoperative radiation was generally done. In patients with secondary tumors, either locally extensive, or recurrent rectal adenocarcinoma or epidermoid carcinoma of the anorectum, preoperative therapy was given unless the patient had been irradiated previously. Radiation dosages in the 4500 to 5000 cGy range were administered in addition to sensitizing chemotherapy (depending on tumor type): Adriamycin (Adria Laboratories, Columbus, OH) with sarcomas, 5-fluorouracil/cisplatinum or mitomycin C combinations for adenocarcinoma or epidermoid cancer to facilitate surgical control.[2,16,17]

In the current study, the following chemotherapy protocols were used:

Primary sarcomas. Radiation 3000 to 3500 cGy in 10 to 15 fractions Adriamycin 30 mg/day × 3 with continuous infusion (as radiation sensitizer)

Recurrent rectal adenocarcinoma. Radiation 4500 to 5000 cGy in 20 to 25 fractions (if not previously treated), and sensitizing 5-fluorouracil 750 mg/M^2/d × 5

Advanced epidermoid cancer. Radiation 3000 cGy, in 15 fractions plus 5-fluorouracil 750 mg/M^2/d × 5, and mitomycin C 15 mg/M^2 × 1

Patient Population

A total of 76 patients were treated, including 18 with primary tumors and 58 with secondary tumors involving the true pelvis (Table 1). Among the 18 patients with primary tumors, there were eight women, 10 men, average age 47 years. In all but two patients, there was involvement of the musculoskeletal elements of the pelvis by the visceral tumor necessitating a composite resection. Special approaches were required for access to and safe removal of the tumor in two patients with extensive soft tissue sarcoma. Patients with extensive cancers who had visceral resections only, such as exenteration, were excluded from this review.

Primary posterior pelvic tumors that invaded the sacrum included three chordomas, three schwannomas, and one of each of the following: osteosarcoma, malignant giant cell tumor, chondrosarcoma, liposarcoma, neurosarcoma, and synovial sarcoma. Two patients had massive presacral space tumors; one hemangiopericytoma and one very extensive liposarcoma. These two required access by an abdominal inguinal incision and one had removal of the accompanying internal iliac artery and vein, to facilitate wide-field resection. Three had lateral pelvic tumors (ileum and ischium), and one patient had primary chondrosarcoma of the symphysis pubis.

Among the secondarily involving cancers of the posterior pelvis, two patients had advanced primary rectal cancer,[2] and 45 had recurrent rectal adenocarcinoma.[4,5] Six had palliative resections, and 41 had resection with curative intent (Table 1).

These patients included 17 women and 30 men, with a median age of 56. The characteristics of the 41 patients resected for cure are shown in Table 2 and their previous radiation history in Table 3. In this group, the free interval period (time to recurrence) was 23 months. Twenty-three patients (56%) had previous abdominoperineal resection, and the remaining had a sphincter-saving procedure. Their initial stage was Dukes A in 1, B2 to B3 in 18 patients, and Dukes C in 17 patients. In five, the Dukes stage was unknown. The palliative resections (with known extrapelvic disease) were done in patients who had large bulky tumors that were infected, had fistulized, or had developed open ulcerated, painful, malodorous lesions. In such cases, there was disease outside of the true pelvis.

The CEA level was < 5 ng/mL in 16 patients and > 5.0 ng/mL in 18 patients. Among the latter, 36% were 5 to 20 ng/mL, 45% were 21 to 100 ng/mL, and 9% were > 100 ng/mL. In seven patients, the preoperative CEA levels were unavailable.

TABLE 1. *Extensive Pelvic Tumors: Secondary Tumors (n = 58)*

Tumor	No.
Posterior pelvis	55
Advanced/recurrent rectal cancer	47
Curative	41
Palliative	6
Epidermoid cancer	8
Advanced anorectal	7
Advanced cervix	1
Lateral pelvis	2
Locally advanced	
Cervix cancer	1
Anorectal cancer	1
Symphysis pubis	1
Locally advanced bladder cancer	

TABLE 2. *Rectal Cancer: Pelvic Recurrence, Resections, and Curative Intent*

	No. of Patients
Patient characteristic	
Age (mean) 59 yr	
Sex (M/F) 26/15	
Free interval time to recurrence (median) 23 mo	
Time with recurrence (median) 5 mo	
Previous surgery	
Anterior resection	16
Abdominoperineal resection	20
AR → APR	2
APR → exenteration	1
Fulguration alone	1
None	1
Original Dukes stage (Astler–Coller)	
A	1
B2	15
B3	3
C	17
Unknown	5
CEA level	
≤5 ng/mL	16
>5 ng/mL	18
N/A	7

AR, anterior resection; APR, abdominoperineal resection.

TABLE 3. *Pelvic Recurrences: Previous Irradiation and Curative Resections*

Irradiation	No. of Patients
None	3
3000–4500 cGy	16
5000–6000 cGy	16
6000–7000 cGy	2
>7000 cGy	2
Unknown	2

For purposes of comparison, a group of 30 patients with recurrent rectal cancer has been reviewed (details previously reported)[16] who were treated with irradiation ± chemotherapy without resection. This included 14 men and 16 women, mean age, 60 (range, 33 to 80 years) Previous surgery included abdominoperineal resection, 24 patients, and low anterior resection, six patients. Original stage was A or B in two patients, classic Dukes B in 13 patients, and Dukes C in 15 patients.

Among the patients with epidermoid cancers that invaded the sacrum were seven with advanced anorectal cancer, and one cervical epidermoid cancer. An additional two patients, one with cancer of cervical, the other with cancer of anorectal origin, had involvement of the posterior and lateral pelvis, and one patient with a bladder cancer had involvement of the symphysis.

Operative Procedures

The operative approach was determined by the extent and nature of the primary tumor.[16] In patients with primary tumors of the sacrum, a laparotomy was required to separate the rectum from the presacral tumor and to devascularize the posterior pelvis. In patients with recurrent rectal cancer or advanced cervical carcinoma, the abdominal approach commonly included a pelvic node dissection and frequently an exenteration in conjunction with the posterior resection (Table 4).

During the posterior approach, a laminectomy was done to visualize the dural sac and the nerve roots. The nerve roots were dissected free at the level of sacral resection, and preserved if there was no gross tumor involvement. For large pelvic schwannomas, most of the posterior nerve roots not involved by tumor could be dissected free and preserved. In the case of primary large tumors of the sacrum (chordoma or sarcoma) or recurrent rectal carcinoma, an *en bloc* resection was required, which included the sacral nerve roots at the level of the tumor.

Results

Recurrent Rectal Cancer Group

Among the patients resected for recurrent rectal carcinoma, 41 were resected with curative intent and six for palliation. In the palliative group, resections were done to control unremitting local disease and, although efforts were made to obtain clear margins, disease beyond the pelvic resection site precluded curative resection. Twenty-two patients required an exenteration or had other organs resected in conjunction with the sacrum. In 36 patients, the surgical margin was clear, and in five there was microscopic involvement in spite of gross clearance of the tumor. The blood loss and operative time is shown in Table 5. In most of the rectal cancer patients, a staged procedure was done (the anterior phase usually requiring 10 hours and the posterior approach 5 to 6 hours). Of patients with long-term follow-up (>6 months), 30 of 31 (96%) had relief of initial symptoms, pain, mass, or fistula. Overall, 23 of 35 patients (66%) returned to previous lifestyle, and 12 of 28 returned to work.

TABLE 4. *Pelvic Recurrence: Extent of Resection and Curative Intent*

Extent of Resection	No. of Patients
Other organs resected	
Rectum	15
Bladder*	23
Partial bladder resection	1
Prostate/seminal vesicles	16
Vagina	7
Total abdominal hysterectomy	4
Segmental bowel resection	6

* All required ileal conduit.

TABLE 5. *Pelvic Recurrences: Operative Details and Curative Resections*

Operative blood loss	
Estimated blood loss	10,000 mL mean 8000 mL median
Replaced blood volume	20 units mean 15 units median
Operative time	
18.5 hr mean	
18.0 hr median	

Survival

Of the six patients who had palliative resections, the survival ranged from 2 to 12 months (2, 4, 8, 9, 11, 12 months). In the 41 patients resected for cure, the median disease-free survival was 24 months, overall median survival was 36 months, and the 5-year estimated survival was 24% (Figs. 1, 2). There were five patients surviving 67 to 168 months (Table 6). In comparison, in the group of 30 patients with rectal recurrence treated by irradiation, the median survival was 15 months, with 5-year survival of 3% (Fig. 2).

Epidermoid Cancer Group

In the group with epidermoid carcinoma (Table 6), seven had advanced anorectal cancers requiring abdominal sacral resections. All had been pretreated with a regimen of chemotherapy and radiation before operation. One patient developed a second tumor (carcinoma of the gallbladder) that was the cause of death at 28 months. An additional patient with recurrent epidermoid carcinoma required a hemipelvectomy to control disease in the posterior lateral pelvis, and died of disease within 9 months. Two patients were resected for recurrence of cervical cancer involving the posterior pelvis or posterior and lateral pelvis. One is surviving at 48 months with no evidence of disease after hemisacrectomy; the other patient died after 12 months of metastatic cancer after hemipelvectomy. One patient with a bladder cancer that invaded the symphysis pubis died of numerous complications 90 days after composite resection of the central portion of the pelvis.

Primary Tumors

In the entire group of patients resected for primary tumors of the pelvis, the estimated survival was 52% at 5 years (Fig. 3). The actual survival is listed in Table 7.

Level of Sacral Resection

Among the primary tumor group were two patients with resections at L5–S1 and between L3 and L4. All of the carcinoma patients had resections between S1 and S2 or lower. Three patients had unilateral hemisacrectomy with nerve preservation (Table 8).

Mortality Rate

In the 47 patients resected for pelvic recurrence of rectal cancer, four (8.5%) had perioperative deaths. One patient died of a platelet-induced coagulopathy and myocardial infarction 24 hours after surgery. There were three delayed hospital deaths at 35, 40, and 52 days from cerebrovascular accident (1 patient), and multisystem organ failure (2 patients). One patient died after removal of a recurrent bladder cancer involving the symphysis pubis at 90 days among the 11 patients grouped as "epidermoid cancers." One patient died of a postoperative myocardial infarction at 48 hours after sacrectomy for a chordoma. The total long-term hospital mortality rate was 6 of 76 patients (7.3%).

Morbidity Rate

In the 58 patients having abdominal sacral resection for recurrent or advanced epidermoid or rectal cancer, major complications were cardiopulmonary insufficiency

TABLE 6. *Status of Patients With Secondary Tumors of the Posterior Pelvis*

Secondary Tumor		Procedure		Patient Status			Long-term Survivors	
Type	No. of Patients	Type	No. of Patients	Status	No. of Patients	Duration of Follow-up (mo)	Status	Duration of Follow-up (mo)
Rectal adenocarcinoma	47	Resection with curative intent	41	NED	10	36*	NED	168
				DOD	22		NED	103
				DOC	4		DOD	82
				LWD	1		LWD	75
				POD	4		NED	67
		Palliative resection	6	DOD	6	(2, 4, 8, 9, 11, 12 mo)	—	—
Epidermoid carcinoma of the anorectum	8	Resection with curative intent	8	DOD	6	(7, 9, 11, 13, 24, 28 mo)	NED	
				DOC	1	(7 mo)		
				NED	1	(153 mo)	NED	153

* Median.

NED, no evidence of disease; DOD, dead of disease; DOC, dead of other cause; LWD, living with disease; POD, postoperative death.

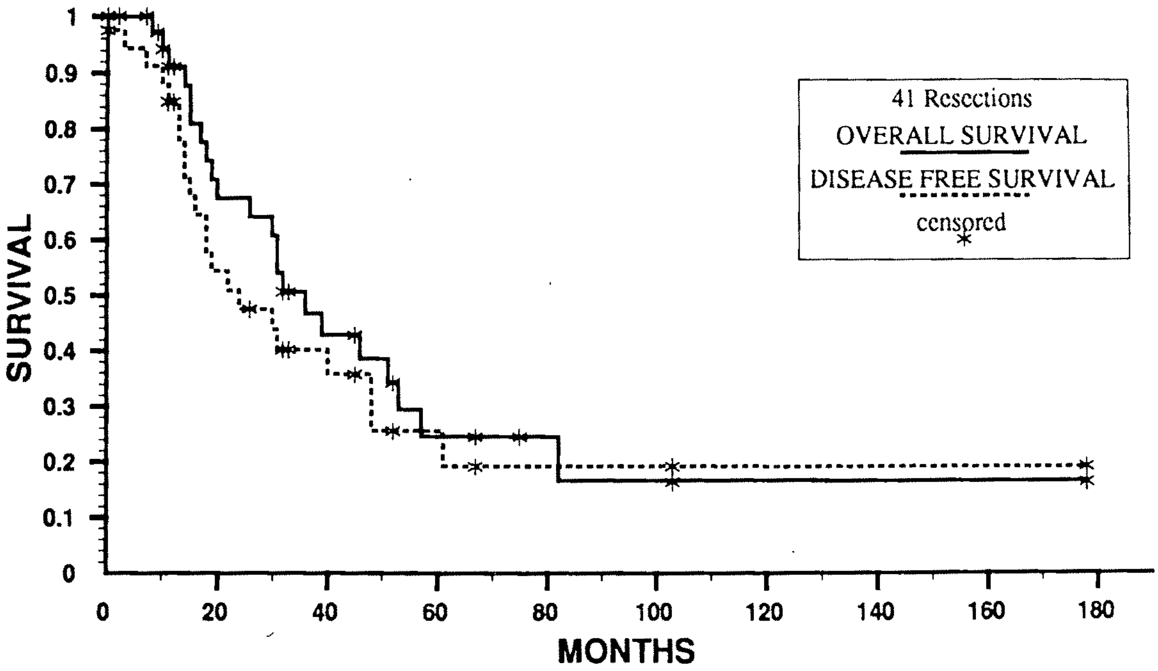

FIG. 1. The median disease-free survival was 24 months, and the overall survival was 36 months in 41 patients who underwent resection of recurrent rectal cancer with curative intent.

requiring prolonged intubation in 10, postoperative hemorrhage requiring a return to the operating room in six patients, and renal failure in five patients. Fistulization of the bowel occurred in eight patients and of the ureter and bladder in three patients. Sepsis was recorded in 14 patients. A variety of wound complications occurred: wound infection (11 patients) and flap separation (16 patients), all in patients who had been heavily irradiated (Table 9). Among the patients resected for primary pelvic tumors, markedly fewer complications occurred. The operative procedure is shorter and most were not irradiated. In the overall group, perineal nerve palsies occurred in

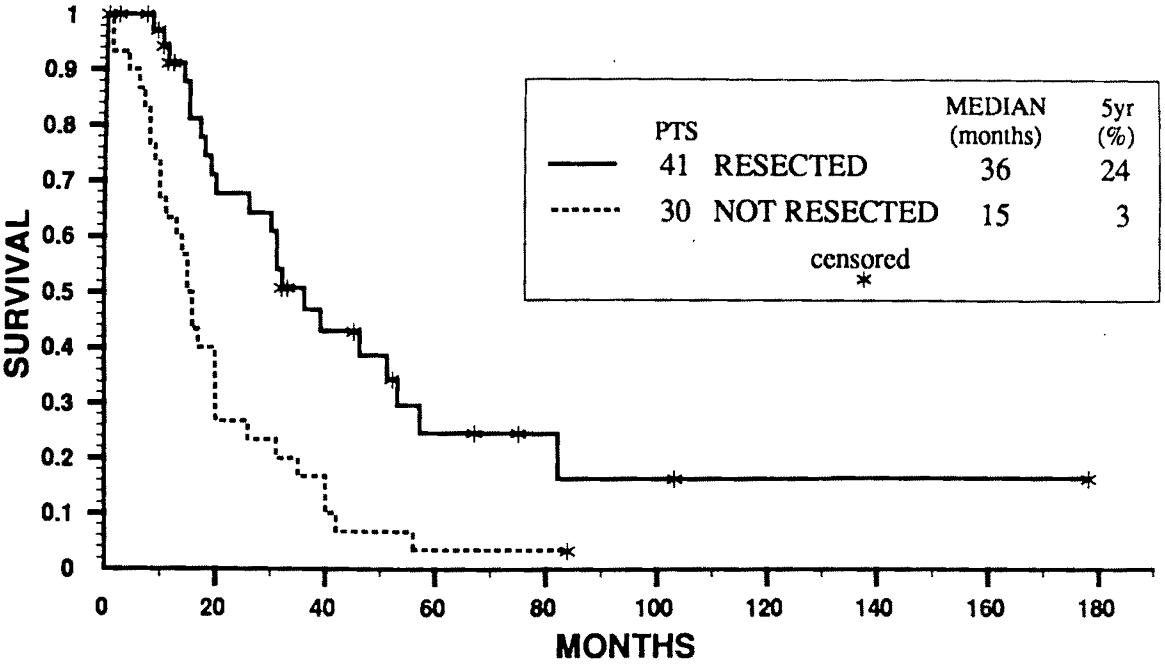

FIG. 2. Estimated 5-year survival was 24%, and median survival was 36 months after resection of recurrent rectal cancer in 41 patients compared with 3% and 15 months median survival in 30 patients treated by radiation alone. $p < 0.001$.

TABLE 7. *Status of Patients With Primary Tumors of the Posterior Pelvis*

Primary Tumor	Age	Sex	Patient Status	Follow-up (mo)
Chordoma	58	F	DOD	179
	70	M	POD	—
	55	M	DOD	30
Schwannoma	46	F	DOD	15
	27	M	NED	26
	40	M	NED	14
Liposarcoma	70	M	DOD	13
	83	F	DOD	25
Osteosarcoma	20	M	DOD	19
Chondrosarcoma	54	F	NED	136
Neurosarcoma	40	F	NED	48
Synovial sarcoma	22	F	DOD	27
Giant cell tumor	45	M	NED	92
Hemangiopericytoma	38	M	NED	27
Lateral/posterior pelvis				
Liposarcoma	70	F	DOD	16
Giant cell tumor	47	F	NED	101
Giant cell tumor	45	F	NED	69
Chodrosarcoma	63	M	NED	112

DOD, dead of disease; POD, postoperative death; NED, no evidence of disease.

five patients and one patient had a femoral nerve injury secondary to ischemia associated with an occluded right femoral artery. Six patients had documented venous thromboses, but no recognized episodes of pulmonary embolism.

Functional Results After Sacrectomy

The functional results after resection in patients with primary posterior pelvic tumors depended on the extent and level of sacral resection (Table 10). Anorectal function was normal in patients having low sacral resections (at or distal to the S3 level) or in patients who had unilateral resection of sacral roots. Anorectal and urogenital function was compromised by bilateral resection levels of S3 and above. One male patient who had resection of the S2 and 3 nerve roots on one side had essentially no deficit of urogenital or anorectal function. A second male patient who had a hemisacrectomy with preservation of S1, S2, and S3 on one side had moderate retention of urogenital function; in other words, bladder tone was good, and he had sensation of bladder distention at 200 mL, but did not have erectile capacity and had essentially absent anorectal tone and anorectal function. A woman with hemisacrectomy involving sacral roots S1 through S5 had numerous rectal and urologic problems mostly related to fistulae in irradiated tissue. She did have persistent leg weakness (S1 root removal). Generally, female patients had less urinary retentive problems, for anatomic reasons. Patients with resection at the S1, S2 level could manage urologic function by practicing Credé at defined periods. In male patients with a high sacral resection, (through the S1 level), periodic catheterization was additionally required. In some cases, the patients did have incontinence, which was improved by taking ephedrine. One patient after resection of sacral chondrosarcoma had persistent incontinence and required placement of a periurethral device for control with moderate effectiveness (this required subsequent removal because of infection). The patients with impairment of anorectal function could be managed by rectal irrigation every other day to control

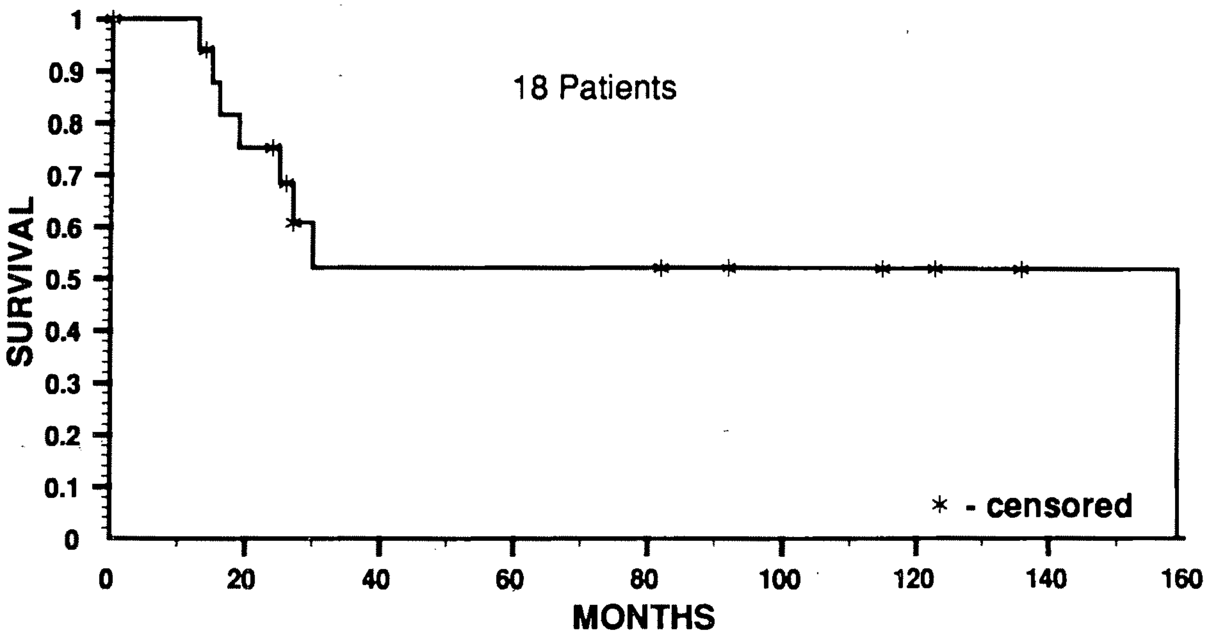

FIG. 3. Survival in patient with primary pelvic tumors after abdominal sacral resection. Median survival is not yet reached. Estimated 5-year survival was 52%.

TABLE 8. *Posterior Pelvic Tumors: Sacral Resection Level*

Primary Tumors		Secondary Tumors*	
L3–4	1	S1–2	47
L5–S1	1	S3	5
S1–2	7	S4–5	2
Partial removal			
S2–5	1*	S1–5	1*
S2–5	1*		

* Hemisacrectomy.

bowel function. The practice of Kegel (natural birth exercises) possibly aided rectal tone. The problem of impotency was managed by urologic placement of a penile prosthesis.

Long-term functional results were evaluable in 35 of 41 patients having curative resection of recurrent rectal cancer. These patients all had pain in the perineum or perineal area before resection. In all but one patient (30/31), there was relief of this burning, boring pain. In 12 patients, however, this pain was replaced with a secondary pain related to the surgery, either a phantom pain or a musculoskeletal pain, or sciatic pain (causalgia): these symptoms generally abated within 3 months. All patients were referred for rehabilitation and generally required physical therapy in a rehabilitation center and subsequent aggressive outpatient therapy.

Discussion

This report has emphasized the role of surgical extirpation of primary or recurrent malignancy that involves the major musculoskeletal elements of the posterior or posterolateral pelvis. Although these are diverse tumors, surgical considerations are similar. Whatever the tumor type, it is essential to obtain microscopically clear margins with resection. In patients resected for pelvic recurrence of rectal cancer in which all disease is resected (curative intent), the actuarial survival was 24%, and five patients survived beyond 5 years. These results are paralleled by other reports,[18,19] and suggest that in well-selected patients with advanced primary or recurrent rectal cancer, complete removal of the tumor by abdominal sacral resection can achieve respectable long-term control rates. The long-term results are similar to those reported after resection of liver metastases from colorectal cancer.[20] The results of resection of advanced epidermoid carcinoma that is fixed in the pelvis and invades the bony elements are less favorable (approximately 15% survival). Although patients with early epidermoid carcinoma of the anorectum generally have high response rates to chemotherapy and radiation (frequently obviating need of radical resection), those with very large tumors are less responsive and require extended resections to obtain local control.[17] Recurrent epidermoid cancers of the cervix rarely present with isolated pelvic bone invasion. Selected patients may merit an aggressive resection (one of two patients in this series is surviving with no evidence of disease for more than 48 months). In patients with primary sacral tumors, either chordoma or sarcoma or the variety of giant cell tumors that occur in this region, resection with complete removal of the tumor is possible by abdominal sacral resection by the lateral approach[21] or by a combination of these approaches, as used by various authors.[4–7,11–13]

The management of extensive pelvic tumors commonly requires interaction among surgeons from different disciplines to effectively accommodate total tumor removal, reconstruction, and restoration of function. Rehabilitation is a major portion of the postoperative care, and most patients require a comprehensive rehabilitation program.

Because of the high risk for recurrence, multidisciplinary therapy is essential, depending on tumor type, the stage of disease, and whether a primary or recurrent tumor is involved. The patients with primary sarcomas, when

TABLE 9. *Mortality and Complications After Resection of Tumors of the Musculoskeletal Pelvis*

	Rectal Adenocarcinoma (n = 47)	Epidermoid Carcinoma (n = 11)	Primary Tumors (n = 18)
Perioperative mortality	4 (8.5%)	1	1
Complications			
Cardiovascular			
Myocardial ischemia, arrhythmia	2	1	0
Pneumonia	2	0	0
Pulmonary insufficiency (prolonged enterbation/ARDS)	8	2	0
Intraoperative coagulopathy	1	0	2
Postoperative hemorrhage	6	0	3
Fistula			
Small bowel/large bowel	5	3	1
Bladder/ureteral	3	0	2
Infection			
Sepsis	14	1	0
Urinary tract	5	0	0
Wound complications			
Wound infection	7	5	1
Posterior wound infection/flap separation	15	1	1
Bowel/urinary			
Small bowel obstruction	4	0	0
Renal failure	5	0	1
Hydronephrosis, ureteral stricture	0	1	0
Urinary incontinence	0	0	3
Urinary retention	0	0	1
Vascular/nerve			
Perineal nerve palsy	3	1	0
Deep venous thrombosis	2	2	2
Arterial transection/ischemia			
Myonecrosis	0	0	1

TABLE 10. *Function After Posterior Resection for Primary Tumors*

Sacral Resection Level	Age	Sex	Sensory Locomotion	Function 0–4 (normal)		
				Anorectal	Bladder	Sexual
L3–4	20	M	Lower extremity paralysis Has hip flexion Anesthesia below hip	0	0	0
L5–S1	45	M	Plantar flexion Sensation foot/ankle	0–1	1–2	0
S1/S2	48	F	Plantar flexion Sensation foot/ankle	0–1	0–1	NE
S1/S2	55	M	Plantar flexion	0–1	0–1	NE
S1/S2	54	F	None	1–2	0–1	NE
Unilateral S1->5	40	M	Lower leg weakness, transient	0	2	0
Unilateral S2, 3, 4	27	M	Normal leg function	4	4	4
S2–3	24	F	Normal leg function	1–2	1–2	NE

NE, not evaluated.

possible, were treated with a protocol consisting of pelvic radiation 3000 cGy in 10 fractions and a 72-hour continuous infusion of Adriamycin 30 $mg/M^2/d$ (as originally described by Eilber et al.[4]). This therapy was generally well tolerated but was restricted to patients not previously irradiated. This type of protocol, coupled with adequate resection with achievement of microscopically clear margins, appears to have value in the patients with high-grade sarcomas.[2] Perhaps more aggressive chemotherapeutic programs would produce better control of distant disease, although the issue of adjuvant therapy for sarcomas is still controversial.[8]

Patients with locally advanced or recurrent epidermoid carcinoma of the anorectum that presented as massive tumors also were treated with radiation 3000 cGy plus continuous infusion fluorouracil (750 $mg/M^2/d$) for 4 days, plus a single injection of mitomycin C 10 mg/M^2, or injection of cisplatinum (25 $mg/M^2/d \times 3$).[17] Patients with recurrent adenocarcinoma of the rectum generally had been radiated previously. In the event that patients with locally advanced rectal cancer had not been irradiated, we would advocate the use of preoperative radiation 4500 rads plus sensitizing fluorouracil.[22] In general, 4500 to 5000 cGy in conjunction with sensitizing fluorouracil (15 $mg/kg/d \times 3$ days, or continuous infusion dose of 750 $mg/M^2/d \times 4$ days) is well tolerated.

The optimum combined chemoradiation protocol is still not well defined, especially in these patients with locally extensive tumors. Because of the extensive nature of these tumors, the use of preoperative radiation appears obligatory if the patient has not been previously treated, to minimize the chance for recurrence in the pelvis. In this series, all but two of the patients with recurrent rectal cancer had been previously irradiated, and both patients were irradiated before abdominal sacral resection. Thus, nothing could be said about the true benefit of preoperative irradiation with these tumors. The long-term tumor control in patients with advanced cancers of the rectum is a major problem. In this series, there is a high failure rate, with 76% of the patients recurring locally, regionally, or at distant sites. Although there are promising adjuvant therapy data for patients after resection of primary rectal cancer,[22–24] or colon cancer,[25,26] there are no applicable data in patients resected for recurrent colorectal cancer. Continued consultation with oncologists knowledgeable in this area is recommended.

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DISCUSSION

DR. KIRBY I. BLAND (Gainesville, Florida): President Ochsner, Secretary Jones, Fellows and Guests, I rise to congratulate Dr. Wanebo and his colleagues on this presentation, which I think would be appropriately termed a formidable challenge with an aggressive, radical approach to an advanced posterior pelvic malignancy. I thank the authors for the opportunity to review their manuscript in advance, and I recommend to the membership that you review this because it contains a wealth of material that Harry has not had time to present to you. My experience, however, is considerably different in terms of the types of tumors we have approached. The challenge of this operative resection to me is not in the volume of the tumor that presents for resection, but in the anatomic location of the primary or the metastatic lesion. And I think that the overwhelming majority of surgeons nationally, and internationally, for that matter, would consider that adequate resection can be accomplished if three tenets are preserved. And that is, the lesion is midline in the distal or midpelvis; and, secondly, the lesion has a minimal volume, and you can encompass it; and, thirdly, that the lesion does not have a volume that extends significantly to the pelvic sidewalls. If any of these anatomic tenets are breached, I believe that most would deny resection in those patients. Further, I believe that composite resection should not be attempted for patients in whom distant or regional metastases have been documented. And I think, Harry, you have well documented that.

We go through enormous effort to do gastrointestinal series, computed tomography scans of the abdomen and pelvis, magnetic resonance imaging or whatever, to make certain these persons do not have regional or systemic disease, metastatic disease. In fact, we will do computed tomography scans of the chest as well to make certain these patients do not have pulmonary metastases, which as you know are established in about 30% of patients with colorectal primaries. But I now believe that it is inappropriate to embark on a major composite resection for palliative purposes in individuals in whom you cannot expect cure. In my own personal experience of 18 composite resections for posterior midline lesions, 16 of these were adenocarcinomas, advanced adenocarcinoma with primaries or recurrent adenocarcinoma of the rectum, and two leiomyosarcomas, many of whom I have not followed beyond 3 years. We have performed composite resections with curative intent in 14 of these patients and two with palliative intent. Although there were no operative deaths in our series, I must tell you my operative morbidity rate was 100%. In these 16 patients with midline fixed lesions, I was able to perform *en bloc* resections of S2, 3, 4, and 5 coccyx, *en block* with an anterior and a posterior pelvic approach. And as a consequence of sacrifice of S2, 3, and 4, which is the nerve erigentives, and as you know supplies the bladder and prostate, you would expect essentially 100% of men to have major urogenital problems; therefore, these individuals are going to require prolonged catheter intubation, daily intubations, or multiple times or permanent diversions, particularly when the bladder or the prostate are invaded. And I think this is a major consideration in men where they have either recurrent disease or perhaps a T3 or a T4 primary. Still some patients desire the palliative benefit of the procedure because of persistent pain, drainage, or these genitourinary dysfunction symptoms.

Well, I commend you, Harry, on your mortality rate of 8% in these patients with extended resections, in which as we saw in your slides you had a prolonged operative time, over 18 hours. I presume you did this in 1 day, or was that a 2-day operation? How do you do this? You had an enormous blood loss in these cases, and I presume you use cell saver in these individuals. My operative time is much less — again it is a different approach — and I am very conservative about these being midline posterior lesions. I have a couple of questions for you.

I could not determine from your abstract or the paper if there is a difference in resectability as a curative procedure with regard to tumor location. So for similar histologic tumor types, did patients with pelvic sidewall lesions fair worse than individuals who had purely posterior or anterior lesions? Our experience suggests that these are very different operations, and the morbidity and mortality rates are also very different in these patients. And I think you have mentioned to us that in a great percentage of the patients you had given preoperative irradiation. Some of these were failed chemotherapeutic patients. What do you do with a positive surgical margin when you find yourself operating, or do you even attempt to extend those margins with pelvic resection?

The other issue I was very interested in and impressed with was the figures in your manuscript and the slides you have shown us with reconstructions. You have used primarily gluteus medialis cutaneous flaps. I have had a fairly sizable experience with bilateral and single gracilis muscle myocutaneous flaps, which was pointed out to me long ago by Dr. John McCraw of Norfolk. And I have found that this has been very advantageous to fill massive pelvic defects.

And, finally, Harry, I commend you on what I do not believe has previously been achieved or reported. You have reported a 24% long-term survival rate in advanced rectal cancer. That has not previously been reported in my readings. In fact, this exceeds the survival rates for solitary lung and liver metastases from colorectal primaries. So I guess the question I would have is, what is the denominator of your patients in the population in which you have chosen this? I enjoyed the paper, and I thank you for the opportunity to discuss this.

DR. WILLIAM C. WOOD (Atlanta, Georgia): President Ochsner, Dr. Jones Members and Guests, I appreciate the opportunity to have seen this manuscript at the meeting and the privilege of discussing it. I would like to begin by complimenting Dr. Wanebo for assembling this very large series of composite sacral resections so carefully reviewed and reported. I also would compliment him for the points of operative technique that he illustrated so clearly in this manuscript, as he has in his previous manuscripts, which have been helpful to all of us who do these posterior resections. I would say that for me it is easier to do this procedure in an exaggerated lateral position where the patient can be manipulated forward and backward and where I can be in the abdominal cavity and carrying on the posterior resection simultaneously to catch an occasional blood vessel that I might otherwise have difficulty with, which you perhaps do not.

Conceptually and biologically, this report subsumes four different populations. I would like not to comment on the group with epidermoid carcinoma, but on the first group, the patients who have sarcoma. You present 19 sarcomas of the posterior pelvis, given chemoradiation and resection. And the life table survival curve of 18 of those patients is 50% at 5 years and 10 years, which is very commendable.

My first question is that at least two series, from M. D. Anderson and from Massachusetts General, have shown that improved local control has only been associated with radiation levels of 60 to 65 Gy or more. You used half that dose with doxorubicin, and I wonder if you would tell us how that dose was chosen.

Secondly, what was the local control in the patients with sarcomas? We know the survival, but we are not told what the local control rate was. The second population that you describe are these 41 patients with recurrent rectal carcinoma, all but two of whom had had prior radiation. Remarkably, 43% of these patients were able to return to work, and 25% survived 5 years. Now this has already been commented on very capably by Dr. Bland as a superb achievement. It was achieved at no small cost, both of your effort, 18 hours on the average in the operating room, and 20 units of blood. And for that group who benefited, it was most remarkable. Can you from this analysis better help us to identify those patients who will benefit? Or, conversely, from this analysis, can you help us better choose those patients who are not likely to benefit from this very extensive procedure?

Finally, the third group of patients that you describe — or three of the third or the fourth groups — were six patients who had large bulky tumors; infected fistulas; ulcerated, painful, malodorous lesions; you state disease that was present outside the pelvis, and you did this for palliation in these patients. Now those of us who do these procedures know that the patients have several months of recovery and rehabilitation before they are able to be very active at all. These palliated patients survived only 2 to 12 months. Were the symptoms relieved without new symptoms being introduced? And would you still recommend this procedure as a palliative procedure for any group of patients with disease outside the pelvis? Thank you for the privilege of reviewing the manuscript and for the privilege of the floor.

DR. J. BRADLEY AUST (San Antonio, Texas): Dr. Ochsner, Dr. Jones, Members and Guests, I am pleased to have had an opportunity to read Dr. Wanebo's paper before this meeting. Dr. Wanebo has been toiling in these vineyards for a number of years and reported his results as time passed. This paper is in essence a progress report. I concur with what Dr. Bland said and only amplify some of his comments. The radical resectional procedures he is reporting are divided into primarily two groups: primary operations for sarcoma or other locally invasive tumors such as chordomas, 14 in number; recurrent rectal carcinomas, 47 in number; and epidermoid carcinomas, 10 in number. Overall operative morbidity and mortality rates were less than 10%, which is a very fine accomplishment. The current survivors amount to 24%. The 24% that he said were 5-year survivors do not exist; that is a projected figure. But there are 24% of the patients currently alive. This passes the rule of thumb test that the percentage survivors should exceed the in-hospital mortality rate.

Regarding the 14 patients in the sarcoma group, I note three chordomas. I have had an interest in chordomas, which are locally recurring tumors that rarely ever metastasize, and yet there were no survivors in this group. Perhaps, hemicorporectomy should be considered in those tumors with a high potential for local recurrence and low potential for distant spread, particularly if they don't involve S2 or higher, because in my experience, and confirmed by your sacral resections, higher resection leads to loss of bowel and bladder function and disabling difficulties with locomotion. The prolonged rehabilitation required prompts me to advise against hemicorporectomy with tumors with high potential for distant spread. The adjuvant use of radiation therapy or chemotherapy is logical in these patients, but is yet unproven and totally experimental.

Philosophically, the decision to carry out these procedures involves for me three factors. One is the judgment that the proposed procedure is feasible and can encompass the tumor. As far as the recurrent rectal carcinomas were concerned, 41 of 47, this proved true. The second is the technical skill to do the procedure with acceptable mortality and morbidity rates. I suspect that the morbidity rate is the real problem in these patients. Since the operative morbidity rate was significant, with prolonged hospitalization and very prolonged rehabilitation. And the third and probably most important factor is the informed consent of the patient, which details the total picture in an honest, realistic, and compassionate way.

I have a few questions. One, have you considered hemicorporectomy for lesions above S2? Second, were there patients who regretted having these operations? We always talk about the success of our cases and how the patients went back to work, but were there any patients who regretted having the operation? And, finally, I chide you a little bit. You state in your abstract that 25% of 10 patients with recurrent epidermoid cancer had long-term results. Where did you find the half a patient? There were other mathematical glitches, but they do not really detract from the message you have in your paper, Harry. I want to thank the Association for the opportunity to discuss this paper and Dr. Wanebo for presenting the material to us. Thank you very much.

DR. LOREN J. HUMPHREY (Columbia, Missouri): Thank you. I will keep this short because the morning is getting on.

Harry, we have discussed this, and I think what you are doing is pushing the envelope a little further, and over the next decade, we will find out which of those we should not create as another subpopulation.

Do you use mesh in those—not the mesh you use to close posteriorly—but to prevent the bowel from prolapsing down in those that are going to receive radiation after operation? We use a Dexon mesh, and as you know, that will keep the small bowel out for a month. Most of the time we prefer, if it is there, to put the omentum down, and this frequently will effect the same result. My question is really one about lifestyle, and Brad has asked that somewhat. So let me focus on this standpoint. I think the key thing in this more than survival are those 96% that have relief of what I think is the worst pain a cancer patient gets, that pressure posterior on the sacral that they have. You have relieved it 96%. But when it comes back, are they going to go through the same experience as those who were not resected? Thank you.

PRESIDENT OCHSNER: I am really impressed by the number of cases, and it does not take a mathematical genius to realize the amount of time that Harry spends in operating on this large number that it consumed a lot of his young life.

DR. HAROLD J. WANEBO (Closing discussion): I want to thank the discussants for their comments. I will try to be as brief as possible. First of all, Loren, I think you raise a good point. We do use the omentum where possible if it has been preserved. We do use mesh if we cannot use some autologous tissue to cover the pelvic floor, because otherwise there is a potential for herniation. I will include your comment about lifestyle with Brad Aust. That is a very poignant question. The real question is about the informed consent, and I must say that that is very difficult. I have found out that it is not enough for the surgeon to speak to the patient, and so I ask the nurse and our physician assistant to go through the procedure. And this includes — they have both the pictures, which the nurses have put together from previous publications about what the procedure really entails — the patients are taken up to an intensive care unit to see what it is really like to be in an intensive care unit, what it is like to have tubes and things coming out. And even with that though, it is still not enough. I do not think you can adequately explain this to them. I have given the publications to a patient who was a lawyer, and he did read it carefully and did accept the procedure.

You asked whether there are patients that regret having the operation. Yes, we have had some that regretted it. I think the two that come to mind really did badly in spite of everything, and we never really helped them. Even though the initial pain was taken away, we had given them so much misery I do not think we helped them a bit. The point is, however, that almost all of the patients do get relief of that boring pain that is so typical of recurrent rectal cancer. Although you replace some of this with operative pain, it is quite different and can be relieved by nonnarcotics such as Tegretol (Geigy Pharmaceuticals, Ardsley, NY).

Dr. Aust, we have not considered hemicorporectomy, although that may be a necessary procedure in some patients. I think with some new reconstructive techniques you can resect the L4, L5. We have recently done an L3, L4 resection with fibular replacement for the vertebrae. But obviously there are patients in whom maybe this might not be adequate.

Regarding Dr. Bland's comment, I think, Kirby, you point out a very important fact, that the low midline tumors, which are free of the pelvic sidewall, are probably the best to resect. Unfortunately, we do have a fair number of patients with sidewall involvement. There is a way of getting around this, and some of these patients had extended resections, that is, where the endopelvic fascia is included. It is like doing an extended extrapleural pneumonectomy, where you are just within the bony framework, truly outside of all of the basic pelvic fascia. And some of these are survivors, but I think it is a very good question.

Regarding the question about the margins: even when we obtain frozen section of the margins, that is no guarantee, but we do bend over backwards to ensure that we will get complete resection.

Regarding those palliative resections, we have only done one palliative resection in the last 4 or 5 years. We don't think that this procedure is indicated for palliation. I think that about 70 patients with recurrent rectal cancer were considered for surgery. Most of these patients are really highly selected before being explored, but even with that, there are patients who will have disease, *etc.*, found at the time of exploration. I think I did not mention regarding our operative time, which is 18 hours, that we usually stage this. We do the first stage, the abdominal approach for the rectal cancer, on day 1, and then on day 3 we will take the patient back and do the sacral resection part. This is for patients who require an ileal conduit and more extended resection. For the sarcomas, we usually do the entire operation on the same day, and we often use the approach that Bill Wood described, that is, the lateral approach. For these extended procedures involving recurrent rectal cancer, we do not believe there is adequate exposure for the wide field resection with the lateral approach and prefer the prone position.

As for that dosage, 3000 rads with Adriamycin infusion, I think is biologically equivalent to about 5000 rads. And whether higher dosage would be beneficial, I think is a question that would need a trial. I think I have answered most of the questions. Again, I want to thank the membership for first listening and staying late for the papers and also for allowing me to present these data to you. Thank you.

Does Preoperative Radiation Therapy Enhance the Probability of Local Control and Survival in High-risk Distal Rectal Cancer?

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One hundred forty-eight patients were treated with preoperative radiation therapy and surgery for resectable rectal adenocarcinoma at the University of Florida between 1975 and 1986. All patients had at least 5 years' follow-up; no patient was lost to follow-up. Three treatment protocols were used over the study period: 1975 to 1978, 3500 cGy in 20 fractions; 1979 to 1983, 4000 to 5000 cGy at 180 cGy per fraction; and 1984 to 1986, 3000 cGy in 10 fractions. The change was made to 3000 cGy in 10 fractions to reduce the inconvenience and expense associated with preoperative radiation therapy without sacrificing any improvement in local control or complication rates. There were no significant differences in the rates of local control, absolute survival, cause-specific survival, or complications between the three preoperative radiation therapy protocols. The results were compared for the 132 patients who underwent complete resection after preoperative radiation therapy and a series of 135 patients who underwent a complete resection alone for adenocarcinoma of the rectum at the University of Florida between 1959 and 1976. The results at 5 years, calculated by the product-limit method, for preoperative radiation therapy and surgery compared with surgery alone, respectively, were as follows: for local recurrence-free survival, 96% and 67%; for absolute survival, 66% and 40%; and for cause-specific survival, 77% and 50%. All of these differences are significant ($p = 0.0001$ or less). A subset of 56 patients with locally advanced lesions, based on tethering or circumferential involvement of the rectal lumen, treated with preoperative radiation therapy and surgery were compared with patients treated with surgery alone for stage B2 and C cancers. There was a significant improvement in local control and survival rates in the group irradiated before operation. There was no apparent increase in the incidence of postoperative complications in the patients irradiated before operation.

THE DOCUMENTED INCIDENCE of local recurrence after surgery alone for adenocarcinoma of the rectum and rectosigmoid is substantial (Table 1).[1-6] Local recurrence-free survival, calculated by the product-limit method,[7,8] for a series of 135 patients treated with surgery alone at the University of Florida for adenocarcinoma of the rectum and rectosigmoid is depicted in Figure 1. Thirty-five patients (26%) developed recurrent disease in the pelvis or perineum; 19 (54%) of 35 either died of disease or were alive with disease at last follow-up without evidence of distant metastasis.[1] Preoperative radiation therapy has been used since 1975 at the University of Florida for patients with clinically resectable rectal cancer to decrease the risk of local recurrence and to enhance the probability of cure.[9,10] The investigators began the use of a short course of moderate-dose radiation therapy, 3000 cGy in 10 fractions over 2 weeks, substituted for 4500 cGy in 25 fractions over 5 weeks, in an effort to reduce the overall treatment time and expense associated with preoperative radiation therapy. The new treatment protocol was based on the experience of Professor Jean Papillon and the use of 3000 cGy in 10 fractions before interstitial implantation for T1 and T2 squamous cell carcinoma of the oral tongue.[11,12] Radiobiologically, 3000 cGy in 10 fractions is probably equivalent to 4500 cGy in 25 fractions. The first patient was treated with this new protocol in November 1983. Because of concern about the effect of the intense, short-course radiation therapy on the integrity of a subsequent anastomosis after anterior resection, patients treated with this protocol were those in whom the anticipated surgical procedure was abdominoperineal resection.

The purpose of this report is twofold: to report the results in patients treated with the moderate-dose, short course of preoperative radiation therapy and to compare

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TABLE 1. *Incidence of Local Recurrence With Surgery Alone (5-year Minimum Follow-up)*

Author and Institution	Site	A	A/B1	B1	B2	C1	C2	Total
Mendenhall et al.[1] University of Florida	R, RS	0/14	—	5/23 (22%)	10/45 (22%)	9/24 (38%)	11/29 (38%)	35/135 (26%)
Malcolm et al.[2] Peter Bent Brigham Hospital	R, RS, S	1/16 (6%)	—	6/62 (10%)	12/36 (33%)	5/20 (25%)	9/22 (41%)	33/156 (21%)
Walz et al.[3] Washington University	R, RS	2/15 (13%)	—	0/22 (0%)	7/50 (14%)	2/8 (25%)	15/48 (31%)	26/143 (18%)
Pilipshen et al.[4] Memorial Sloan Kettering	R	0/5 (0%)	—	18/128 (14%)	32/111 (29%)	11/49 (22%)	44/89 (49%)	105/382 (27%)
Rich et al.[5] Massachusetts General Hospital	R, RS	—	3/39 (8%)	—	18/59 (31%)	2/4 (50%)	20/40 (50%)	43/142 (30%)
Veazey and McBride[6] M.D. Anderson Hospital	R	—	3/37 (8%)	—	6/27 (22%)	17/58 (29%)		26/122 (21%)

Modified from Mendenhall WM, Million RR, Pfaff WW. Patterns of recurrence in adenocarcinoma of the rectum and rectosigmoid treated with surgery: implications in treatment planning with adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 1983; 9:977–985.

R, rectum; RS, rectosigmoid; S, sigmoid.

the results in patients irradiated before operation with those of patients treated with surgery alone at the University of Florida before the routine use of preoperative radiation therapy. A subset of patients with locally advanced lesions, based on tethering or complete circumferential involvement of the rectum, treated with preoperative radiation therapy is compared with patients with B2 and C lesions treated with surgery alone.

Materials and Methods

One hundred eighty-nine patients were treated with preoperative radiation therapy for adenocarcinoma of the rectum and rectosigmoid at the University of Florida between August 1975 and April 1986; 148 patients (78%) had lesions that were thought to be clinically resectable and form the basis of this report. A lesion was defined as clinically resectable if it was mobile, tethered (*i.e.*, exhibiting reduced mobility), or not palpable on rectal examination. Lesions that were definitely fixed to structures such as the sacrum, pelvic sidewall, prostate, or bladder were defined as clinically unresectable and were not included in this analysis.[13] Direct extension to the uterus or vagina did not denote clinical unresectability. All patients were observed for 5 or more years after treatment; no patient was lost to follow-up. Patients were staged according to the Astler-Coller modification of the Dukes staging system.[14,15]

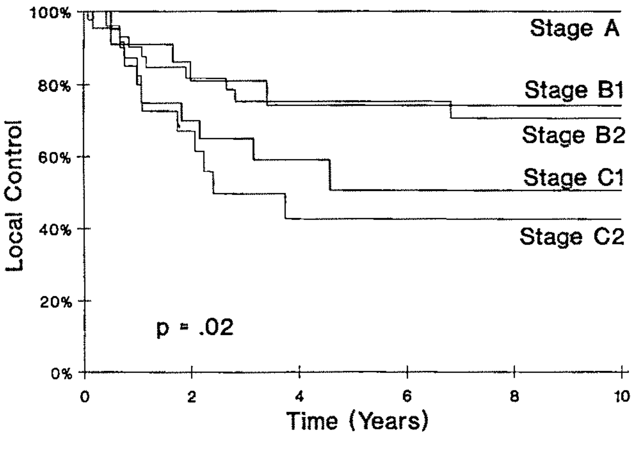

FIG. 1. Local control after surgery alone (135 patients).

All patients underwent a chest roentgenogram, hemogram, and liver function tests before treatment. In addition, the following studies were obtained: barium enema, 85%; intravenous pyelogram, 56%; computed tomography of the abdomen and pelvis, 37%; liver-spleen scan, 35%; colonoscopy, 21%; bone scan, 8%; and cystoscopy, 3%. The pretreatment characteristics of the primary tumor are listed in Table 2.

Between approximately 1975 and 1978, 28 patients were treated with 3500 cGy in 20 fractions, five fractions per week, and one patient received 3100 cGy in 12 fractions, three fractions per week, over 4 weeks. In 17 (59%) of 29 patients, the perineum was treated with an additional "boost" dose of 500 cGy to 600 cGy in two to three fractions. After it became apparent that this regimen was well tolerated, the dose was increased to 4000 cGy to 5000 cGy at 180 cGy per fraction, five fractions per week. This treatment schedule was used for 78 patients treated between approximately 1979 and 1983 (of whom 69 patients received 4500 cGy in 25 to 26 fractions). Eleven (14%) of 78 patients received a perineal boost in addition to the above treatment. In November 1983, the first patient was treated with the new treatment protocol of 3000 cGy in 10 fractions, one fraction per day, over 2 weeks. This treatment schedule was used to treat 41 patients and was restricted, with one exception, to those patients in whom the anticipated surgical procedure was an abdominoperineal resection. Patients treated after 1983 in whom the planned procedure was an anterior resection received 4500 cGy in 25 fractions.

TABLE 2. *Prognostic Factors for 148 Patients*

Parameter	Treatment Group: 3100–3500 cGy (29 patients)	4000–5000 cGy (78 patients)	3000 cGy/10 Fractions (41 patients)	Total (148 patients)
Distance from anal verge (cm)				
0–6	14 (48%)	45 (58%)	25 (61%)	84 (57%)
7–12	13 (45%)	29 (37%)	16 (39%)	58 (39%)
13–18	2 (7%)	3 (4%)	0	5 (3%)
No data	0	1 (1%)	0	1 (1%)
Length of lesion (cm)				
0–4	16 (55%)	31 (40%)	27 (66%)	74 (50%)
5–8	13 (45%)	37 (47%)	11 (27%)	61 (41%)
≥9	0	2 (3%)	0	2 (1%)
No data	0	8 (10%)	3 (7%)	11 (8%)
Histologic differentiation				
Well	3 (10%)	12 (15%)	3 (7%)	18 (12%)
Moderate	20 (69%)	51 (65%)	30 (73%)	101 (68%)
Poor	6 (21%)	11 (14%)	3 (7%)	20 (14%)
No grade	0	4 (6%)	5 (13%)	9 (6%)
Mobility				
Mobile	25 (86%)	43 (55%)	24 (59%)	92 (62%)
Tethered	4 (14%)	31 (40%)	14 (34%)	49 (33%)
No data	0	4 (5%)	3 (7%)	7 (5%)
Annular				
No	16 (55%)	58 (74%)	35 (85%)	109 (74%)
Yes	8 (28%)	16 (21%)	5 (13%)	29 (20%)
No data	5 (17%)	4 (5%)	1 (2%)	10 (6%)

Radiation therapy was administered with a four-field box technique in 147 patients (99%); the remaining patient was treated with a sacral-perineal wedge technique. The field sizes were approximately 10 to 12 cm high and 12 to 14 cm wide for the anterior and posterior fields and approximately 10 to 12 cm in the anteroposterior dimension for the lateral fields.[9] All patients were treated with megavoltage equipment using the following: ^{60}Co, 130 (88%); 17 MV x-ray, 14 (9%); combination of megavoltage beams, three (2%); and 6 MV x-ray, one (1%). In 26 patients (18%) with lesions within 4 cm of the anal verge, the dose to the inguinal lymph nodes was electively boosted, using 10- to 12-MeV electrons, to the same dose level planned for the primary lesion.[16] All patients were treated with planned continuous-course radiation therapy.

The operative procedures were performed an average of 4½ weeks from the completion of radiation therapy (range, 2 to 10 weeks). In 115 patients (78%), the surgery was performed between 3 and 6 weeks after radiation therapy. The procedures that were performed are listed in Table 3. Four patients were not operated on for the following reasons: refused surgery, two patients; distant metastases discovered before the planned operation, one patient; and fatal myocardial infarction before the planned operation, one patient. One of the two patients who refused surgery was 82 years of age and had metastatic prostate cancer at the time that the rectal cancer was diagnosed. No patient received adjuvant chemotherapy.

Acute complications secondary to radiation therapy were scored as follows: minimal, transient, and easily controlled with medications; moderate, persistent but controlled with medications; and severe, requiring an unplanned split in the course of the radiation therapy.[10] Postoperative complications were scored as follows: re-

TABLE 3. *Operative Procedures for 148 Patients*

Operation	Treatment Group: 3100–3500 cGy (29 patients)	4000–5000 cGy (78 patients)	3000 cGy/10 Fractions (41 patients)	Total (148 patients)
Abdominoperineal resection	21 (73%)	63 (80%)	39 (96%)	123 (83%)
Low anterior resection	4 (14%)	9 (12%)	1 (2%)	14 (9%)
Abdominal transsacral resection	2 (7%)	1 (1%)	0	3 (2%)
Hartmann procedure	1 (3%)	0	0	1 (1%)
Total colectomy and proctectomy	1 (3%)	2 (3%)	0	3 (2%)
None	0	3 (4%)	1 (2%)	4 (3%)

quiring a second extra-abdominal operation, requiring a second intra-abdominal operation, and fatal.

Local recurrence was defined as recurrence within the true pelvis or perineum. We previously coded peritoneal seeding and recurrence in the inguinal lymph nodes as local recurrence.[1,9,10] Because most authors restrict the definition of local recurrence to include only disease recurrence in the true pelvis and perineum, however, we have analyzed our data accordingly so that it may be compared with other data in the literature. Sites of disease recurrence reflect the total number of recurrences regardless of when the recurrences were noted, rather than just the first sites of recurrent disease.

Local recurrence-free survival, absolute survival, and cause-specific survival rates were calculated by the product-limit method.[7,8] The significance levels between curves were determined using the log-rank test.[8,17] Patients who underwent an incomplete resection were included in the analysis of complications, but were excluded from analysis of local recurrence and survival so that our series would be comparable to those in which patients were treated with surgery alone or followed by adjuvant radiation therapy or chemotherapy. Even for patients having complete resections, a comparison of those treated with preoperative radiation therapy and surgery and those treated with surgery alone or followed by postoperative adjuvant therapy would potentially still be biased against the patients irradiated before operation. The radiation therapy could conceivably cause a subset of patients originally having incompletely resectable local disease to have completely resectable disease at the time of surgery (*i.e.*, downstaging).

A subset of patients treated with preoperative radiation therapy and surgery were defined as having locally advanced lesions based on tethering (*i.e.*, reduced mobility) or complete involvement of the circumference of the rectum before radiation therapy. The results of treatment of this subset of patients were compared with the results of surgery alone in patients with stage B2 and C cancers.

Results

All patients treated to 3500 cGy in 20 fractions, 3100 cGy in 12 fractions, and 3000 cGy in 10 fractions experienced either no or minimal acute side effects secondar to radiation therapy. Of the 78 patients treated to 400 to 5000 cGy at 180 cGy per fraction, 75 patients experienced no or minimal acute side effects, two suffered moderate side effects, and one experienced severe moist desquamation of the perineum that necessitated an unplanned treatment split. This latter patient was the onl one treated with the sacral-perineal wedge technique. N patient required a diverting colostomy for obstructio during radiation therapy or before the planned operatio after preoperative radiation therapy.

Regression of the tumor, as assessed at the completio of radiation therapy by digital rectal examination, was a follows: none, 6%; 10% to 30%, 33%; 35% to 60%, 23% 65% to 90%, 8%; 100%, < 1%; regressed, percentage unknown, 8%; and no data, 22%.

One hundred thirty-two patients (89%) underwent a apparent complete resection of disease after preoperativ radiation therapy. Incomplete resection was noted in si (21%) of 29 patients treated to 3500 cGy in 20 fraction or 3100 cGy in 12 fractions, seven (9%) of 78 patient treated to 4000 cGy to 5000 cGy, and in three (7%) of 4 patients irradiated to 3000 cGy in 10 fractions. The reasons for unresectability were distant metastases noted a surgery, 10 patients; positive margins, two patients; an no operation, four patients.

The incidence of postoperative complications is show in Table 4 for the patients in this series treated with preoperative radiation therapy in comparison with a serie of patients treated with surgery alone at the University o Florida between 1959 and 1976.[1] There is no obviou difference in the rates of postoperative complications fo the three preoperative radiation therapy regimens. Although the groups of patients are not strictly comparabl because of the different time periods in which they wer treated, there is no apparent difference in the incidenc of postoperative complications for patients treated wit preoperative radiation therapy and surgery compared wit surgery alone.

Five patients (4%) treated with preoperative radiatio therapy and surgery suffered late complications that occurred after the immediate postoperative period. Fou patients experienced small-bowel obstruction necessitatin

TABLE 4. *Postoperative Complications*

	Treatment Group				
Operation	3100–3500 cGy (29 patients)	4000–5000 cGy (78 patients)	3000 cGy/10 Fractions (41 patients)	Preoperative Radiation Therapy Total (148 patients)	Surgery Alon (135 patients
Second extra-abdominal operation required	1 (3%)	4 (5%)	2 (5%)	7 (5%)	8 (6%)
Second intra-abdominal operation required	1 (3%)	5 (6%)	4 (10%)	10 (7%)	9 (7%)
Fatal	0	0	0	0	8 (6%)

operative intervention at 2 months, 6 months, 11 months, and 50 months after treatment. The patient who had bowel resection at 50 months suffered an anastomotic breakdown resulting in fatal peritonitis; this patient represents the only treatment-related fatality in the series. An additional patient had an operation at 1½ years for an enterocutaneous fistula. The radiation therapy schedules used in these five patients were as follows: 3500 cGy in 20 fractions, one patient; 4500 cGy in 25 fractions, three patients; and 4500 cGy in 28 fractions, one patient. In comparing the incidence of late complications of this series with other published data, one must recall that most authors do not report complications that occur after the patient has been discharged from the hospital or that are noted more than 30 days after operation.

Local recurrence was noted in 10 (8%) of 132 patients who underwent an apparent complete resection: three (13%) of 23 patients treated with 3500 cGy in 20 fractions or 3100 cGy in 12 fractions; five (7%) of 71 patients treated with 4000 cGy to 5000 cGy; and two (5%) of 38 patients treated with 3000 cGy in 10 fractions. The local control rates, calculated by the product-limit method,[7,8] for patients treated with the various preoperative radiation therapy schedules, are compared in Figure 2A. There is no apparent difference in the incidence of local control for the three radiation therapy dose-fractionation protocols. The incidence of local control for patients irradiated before operation is compared with that observed after surgery alone in Figure 2B. There is a significant improvement in the probability of local control in the patients irradiated before operation. The 5-year local control rates, calculated by the product-limit method,[7,8] were 97% for preoperative radiation therapy and surgery and 67% for surgery alone (p = 0.0001). The local control rate at 5 years for patients with tethered or annular lesions treated with preoperative radiation therapy and surgery was 93%, compared with 61% after surgery alone for stage B2 and C cancers (p = 0.0001) (Fig. 2C).

The patterns of disease recurrence are listed in Table 5. One patient developed peritoneal seeding in the upper abdomen without evidence of recurrent disease in the pelvis and was coded as having distant metastases. No patient developed recurrent disease in the inguinal lymph nodes. Ten patients developed local recurrence; four of 10 had no evidence of distant metastases at the last follow-up or death. Two patients who developed local recurrence alone underwent salvage surgery, which included a partial sacrectomy in both. One patient is alive and disease free 3 years after salvage surgery, and the other patient is apparently disease free 2 months after the salvage operation. Six of 10 patients who developed local recurrence also developed distant metastases and either died of disease or are currently alive with disease.

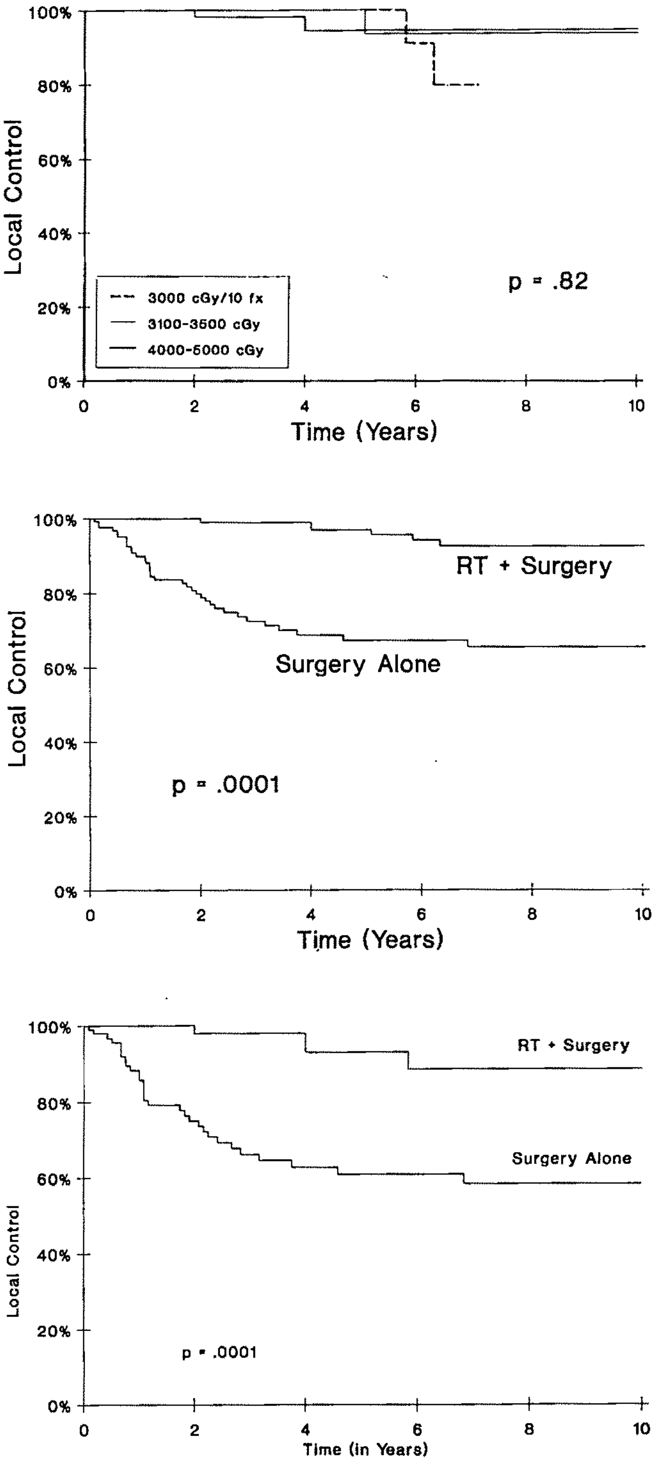

FIG. 2. Local control. (A, top) Preoperative radiation therapy (132 patients). The local control rates at 5 years were 3100 to 3500 cGy, 94%; 4000 to 5000 cGy, 94%; and 3000 cGy in 10 fractions, 100% (p = 0.823). (B, center) Preoperative radiation therapy (132 patients) compared with surgery alone (135 patients). Local control at 5 years was 97% after preoperative radiation therapy and surgery and 67% after surgery alone (p = 0.0001) (C, bottom) Preoperative radiation therapy (56 patients with tethered or annular lesions) compared with surgery (98 patients with stage B2 and C lesions). Local control at 5 years was 93% after preoperative radiation therapy and surgery and 61% after surgery alone (p = 0.0001).

TABLE 5. *Recurrence Patterns for 132 Patients**

Stage	No. of Patients	Local	Local Plus Distant	Distant
0	14	0	0	2 (14%)
A	10	0	0	0
B1	44	0	1 (2%)	8 (18%)
B2	42	3 (7%)	4 (10%)	11 (26%)
C1	6	0	1	0
C2	16	1 (6%)	0	8 (50%)
Total	132	4 (3%)	6 (5%)	29 (22%)

* 132 patients who underwent an apparently complete resection after preoperative radiotherapy.

Four patients underwent attempted surgical salvage of an apparently isolated lung (two patients) or liver (two patients) metastasis. One patient is alive and disease free 3 years after salvage surgery, one patient died disease free 5 years after salvage surgery, and the remaining patients developed a second relapse of disease.

The absolute and cause-specific survival rates, calculated by the product-limit method, are shown in Figures 3 and 4. There are no apparent differences in survival between patients treated with the three preoperative radiation therapy schedules. There is a significant survival benefit for patients irradiated before operation compared with those treated with surgery alone. This is also apparent for the subset of patients with tethered or annular lesions treated with preoperative radiation therapy, compared with patients with stage B2 and C lesions treated with surgery alone. The 5-year survival rates, calculated by the product-limit method, for preoperative radiation therapy and surgery compared with surgery alone, were absolute survival, 66% and 40% (p = .0001); and cause-specific survival, 77% and 50% (p = .0001).

Of the 16 patients who did not undergo complete resection of disease after preoperative radiation therapy, all patients died of disease that was present in the following sites: local alone, three patients; local plus distant, three patients; and distant alone, 10 patients. All four patients who were not operated on after radiation therapy had persistent local tumor at death. Two (17%) of the remaining 12 patients had a local component of disease recurrence at the time of death.

Discussion

Surgery has been the mainstay of treatment for adenocarcinoma of the rectum and rectosigmoid. The gains obtained with adjuvant therapy, although real, are small in comparison with the impact of surgery on the disease process. The goals of adjuvant therapy include decreasing the risk of local recurrence, improving the probability of survival, and allowing patients who would have required an abdominoperineal resection to have a sphincter-sparing

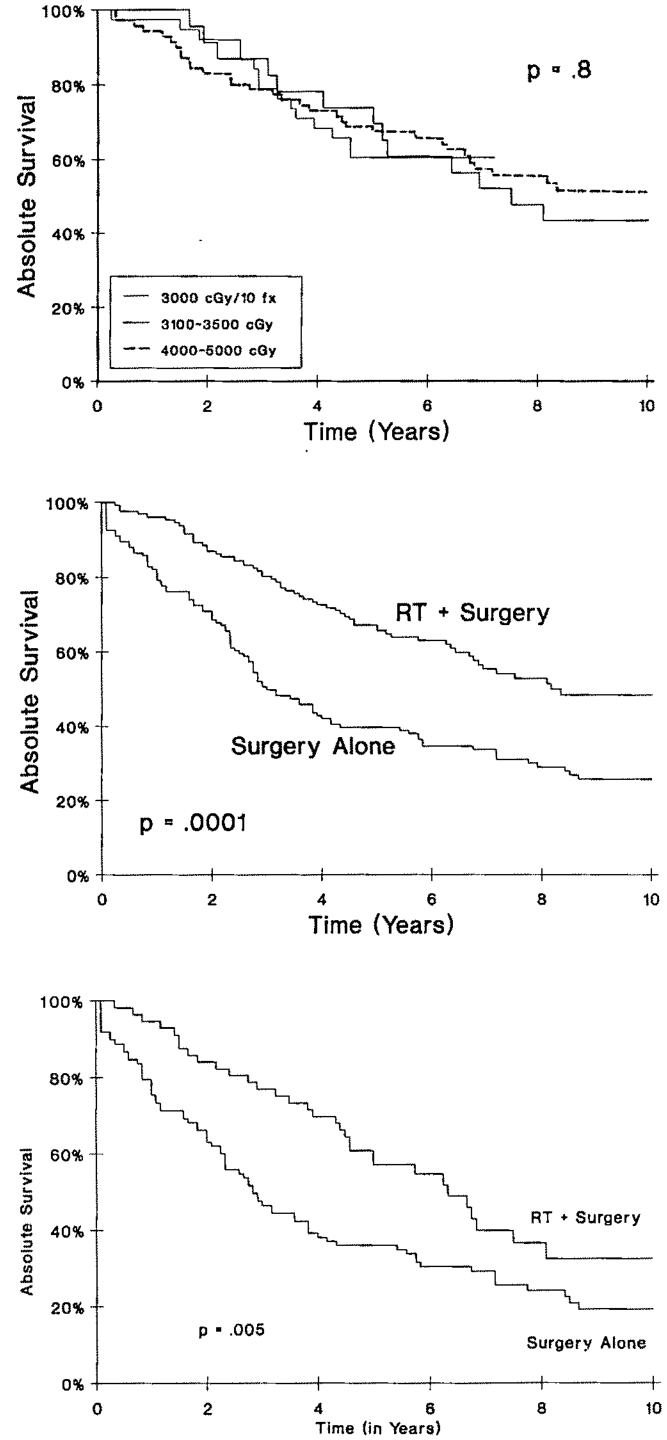

FIG. 3. Absolute survival. (A, top) Preoperative radiation therapy (132 patients). The absolute survival rates at 5 years were 3100 to 3500 cGy, 70%; 4000 to 5000 cGy, 67%; and 3000 cGy in 10 fractions, 61% (p = 0.798). (B, center) Preoperative radiation therapy and surgery (132 patients) compared with surgery alone (135 patients). Absolute survival at 5 years was 66% after preoperative radiation therapy and surgery and 40% after surgery alone (p = 0.0001). (C, bottom) Preoperative radiation therapy (56 patients with tethered or annular lesions) compared with surgery alone (98 patients with stage B2 and C lesions). Absolute survival at 5 years was 61% after preoperative radiation therapy and surgery compared with 36% after surgery alone (p = 0.0054).

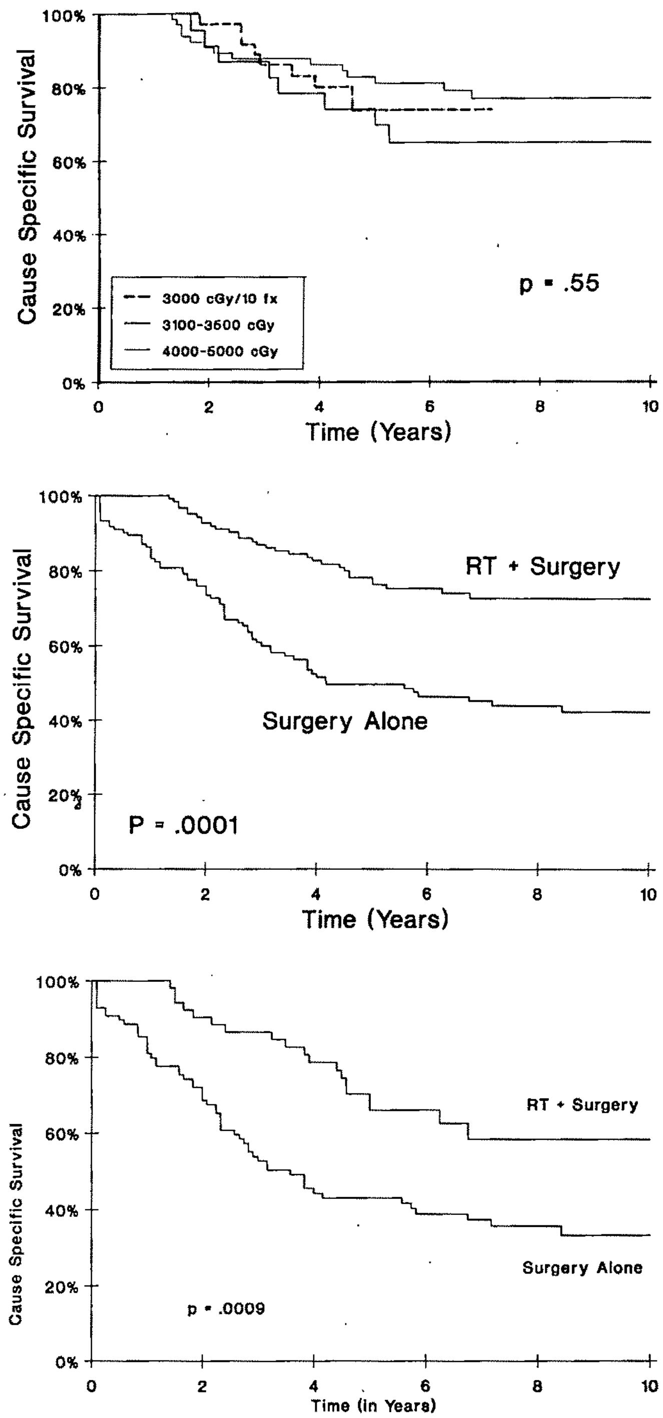

FIG. 4. Cause-specific survival. (A, top) Preoperative radiation therapy (132 patients). The cause-specific survival rates at 5 years were 3100 to 3500 cGy, 70%; 4000 to 5000 cGy, 81%; and 3000 cGy in 10 fractions, 74% (p = 0.555). (B, center) Preoperative radiation therapy and surgery (132 patients) compared with surgery alone (135 patients). The cause-specific survival rates at 5 years were 77% after preoperative radiation therapy and surgery compared with 50% after surgery alone (p < 0.0001). (C, bottom) Preoperative radiation therapy (56 patients with tethered or annular lesions) compared with surgery alone (98 patients with stage B2 and C lesions). Cause-specific survival at 5 years was 66% after preoperative radiation therapy and surgery and 43% after surgery alone (p = 0.0009).

procedure. These goals must be realized with minimal complications, inconvenience, and cost.

Treatment options include surgery alone, preoperative radiation therapy and surgery, surgery and postoperative radiation therapy, and surgery followed by chemotherapy alone or combined with radiation therapy. Each of the above goals of adjuvant therapy will be discussed in the context of the available data. Although preoperative radiation therapy and chemotherapy followed by surgery is an alternative, there is little existing information about this treatment strategy for resectable rectal cancer.

Local Recurrence

There are multiple nonrandomized and randomized trials that indicate that both preoperative and postoperative radiation therapy, either alone or combined with chemotherapy, significantly reduce the incidence of local recurrence compared with surgery alone.[9,10,18-27] Although local control rates after preoperative radiation therapy tend to be better than after postoperative radiation therapy, such a comparison is complicated by the exclusion of pathologic stage A and B1 cancers from the postoperative radiation therapy series and the tendency of most surgeons to select patients with advanced resectable lesions for preoperative radiation therapy. Our data showed that local control at 5 years after preoperative radiation therapy and surgery for the subset of patients with locally advanced lesions was better than has usually been observed after surgery and postoperative radiation therapy for stage B2 and C disease. Pahlman and Glimelius[28] recently reported a multicenter trial from Uppsala, Sweden, in which 471 patients with resectable carcinoma of the rectum and rectosigmoid were randomly assigned to receive either preoperative radiation therapy (2550 cGy in 5 fractions) followed by surgery or an operation followed by postoperative radiation therapy (6000 cGy in 30 fractions, split course) for patients with tumors extending through the muscularis or positive nodes. After a minimum follow-up of 3 years (mean, 6 years), the local recurrence rate was significantly lower in the group irradiated before operation compared with the group treated initially with an operation, 12% *versus* 21%, p = 0.02. Our data and the preliminary data reported by the Stockholm Rectal Cancer Study Group indicate that a moderate-dose, short-course preoperative radiation therapy protocol effectively reduces the risk of local recurrence compared with surgery alone and is probably as effective as a preoperative dose of 4500 cGy in 25 fractions. Although chemotherapy alone does not appear to significantly reduce the incidence of local recurrence, the addition of chemotherapy to postoperative radiation therapy may reduce the incidence of local recurrence compared with that observed after postoperative radiation therapy alone.[26,27,29]

Survival

Although the data are conflicting, the preponderance of the evidence suggests that low-dose preoperative radiation therapy (in the range of 2000 cGy to 3000 cGy at 180 cGy to 200 cGy per fraction) has no impact on survival.[30-34] In contrast, there is some convincing evidence that moderate-dose preoperative radiation therapy, with a dose of approximately 4500 cGy in 25 fractions or its radiobiologic equivalent, may improve survival rates compared with surgery alone.[10,18-20] Gerard et al.[19] reported the results of the European Organization for Research and Treatment of Cancer trial in which patients were randomly assigned to treatment with preoperative radiation therapy, 3450 cGy at 230 cGy per fraction, and surgery or surgery alone for resectable rectal cancer. The 5-year survival rates for the 341 patients undergoing a complete resection were 69% for preoperative radiation therapy and surgery and 59% for surgery alone ($p = 0.08$). Reis Neto, Quilici, and Reis,[20] from the Catholic University of Campinas in Sao Paulo, Brazil, recently reported a series of 68 patients randomly assigned to be treated with preoperative radiation therapy, 4000 cGy in 20 fractions, or surgery alone. Patients were treated between 1978 and 1980, and all were observed for at least 5 years.[20] The authors noted a significant improvement in absolute and cause-specific survival rates at 5 years.

The addition of postoperative radiation therapy to surgery for stage B2 and C rectal cancer has no apparent impact on survival.[27,29] The combination of postoperative radiation therapy and chemotherapy, however, has been shown to improve survival rates for patients with advanced, completely resected rectal adenocarcinoma.[26,27] The NSABP R-01 study showed improved survival rates with postoperative chemotherapy alone but no significant improvement in local control.[29] The chemotherapy regimens that appear to have been effective included combined 5-fluorouracil and semustine, with or without vincristine.[26,27,29] Although semustine is not commercially available because of its leukemogenic potential, a recent clinical announcement from the National Cancer Institute stated that "current preliminary information suggests that substantial treatment benefits may be achieved using radiation therapy and standard doses of 5-fluorouracil" without semustine. O'Connell et al.[35] recently reported an intergroup study in which 453 patients with stage II and III rectal carcinoma were randomly assigned to receive postoperative chemotherapy with 5-fluorouracil or 5-fluorouracil and semustine. Patients also received pelvic radiation therapy and concomitant 5-fluorouracil given either by bolus injection or continuous infusion. With a median follow-up of 16 months, the authors noted that the interim analysis "strongly suggests that MeCCNU does not add to the beneficial effects of 5-fluorouracil plus radiation as surgical adjuvant chemotherapy for stage II and III rectal cancer."[35]

Complications

For patients treated with preoperative radiation therapy in this series, the acute effects secondary to 3000 cGy in 10 fractions appear to be comparable to those resulting from 4500 cGy in 25 fractions. The acute effects of preoperative radiation therapy are substantially less severe than those observed with postoperative radiation therapy for patients undergoing an abdominoperineal resection because it is not necessary to irradiate the perineum in patients treated before operation, thus reducing the volume of tissue irradiated and avoiding desquamation of the perineal skin. The difference in acute effects in patients undergoing anterior resection is not substantially different when comparing preoperative and postoperative radiation therapy regimens.

Our data indicate that the incidence of postoperative and late complications associated with 3000 cGy in 10 fractions is comparable to that observed after 4500 cGy in 25 fractions in patients irradiated before operation, and is similar to that observed in patients treated with surgery alone at our institution. This is in contrast to the data reported by the Stockholm Rectal Cancer Study Group, which showed a significant increase in postoperative morbidity and mortality rates after a short course of intensive radiation therapy as compared with the results of surgery alone.[21] The Stockholm radiation therapy protocol differed from ours in that they used 2500 cGy in five fractions with anterior and posterior fields extending up to the second lumbar vertebra, whereas we used 3000 cGy in 10 fractions with a four-field box technique with the superior field margin located 1 to 2 cm above the bottom of the sacroiliac joint. Recalling that the lowest reported local recurrence rate after preoperative radiation therapy was 0% from the University of Oregon, where 10 × 10 cm fields were used, the unnecessarily large field size and the anterior and posterior field arrangement used in the Stockholm study undoubtedly contributed to the high incidence of complications.[18,21]

The incidence of late complications, particularly small-bowel obstruction, initially was thought to be significantly higher with postoperative radiation therapy than with preoperative radiation therapy.[36] If techniques are employed to minimize the amount of small bowel included in the irradiated volume, however, and the dose is limited to 4500 cGy to 5040 cGy at 180 cGy per fraction, the incidence of late complications after postoperative radiation therapy is probably similar to that observed after preoperative radiation therapy or minimally higher. The addition of chemotherapy to radiation therapy may increase the severity of the acute effects of the radiation therapy if the two are administered concomitantly. Adjuvant chemotherapy does not appear to significantly increase the risk of severe, acute, or late complications.[26]

Use of a Sphincter-sparing Procedure in Patients who Would Have Required an Abdominoperineal Resection

There is a substantial amount of nonrandomized data to indicate that moderate-dose preoperative radiation therapy may be administered safely before anterior resection and that some patients are then able to have a sphincter-sparing procedure rather than the anticipated abdominoperineal resection with an acceptably low risk of local recurrence.[22,37,38]

Cost

Moderate-dose, short-course preoperative radiation therapy, as outlined in this report, is substantially less time consuming and expensive than a 5-week course of radiation therapy combined with chemotherapy. This advantage may be offset by the possibility that some patients with early-stage lesions who do not need adjuvant therapy are included in the group of patients receiving preoperative radiation therapy.

Conclusions

Despite the recommendations of the National Institutes of Health Consensus Conference, two treatment options exist (for patients not entered on clinical trails) that reduce local recurrence rates and may improve survival rates: moderate-dose preoperative radiation therapy and postoperative radiation therapy combined with 5-fluorouracil. We tend to prefer preoperative radiation therapy in patients who clinically appear to have stage B2 or C lesions, because the irradiated volume may be smaller, the possibility of seeding tumor cells at surgery is reduced, the radiation therapy may be more effective because the tumor bed has not been rendered hypoxic by surgical manipulation, and there may be a somewhat lower risk of late complications. A major disadvantage of preoperative radiation therapy is that some lesions are downstaged, thus reducing the accuracy of pathologic staging. Our current policy is to treat patients with lesions that are apparently resectable and locally advanced, based on rectal examination alone or combined with transrectal ultrasonography, with preoperative radiation therapy and surgery. Findings on rectal examination that are indicative of locally advanced disease include tethering and circumferential involvement of the lumen. Patients in whom the anticipated operation is abdominoperineal resection undergo 3000 cGy in 10 fractions; those in whom the planned procedure is anterior resection are treated to 4500 cGy in 25 fractions. We are currently exploring the combination of preoperative radiation therapy and 5-fluorouracil in this setting. Patients with less locally advanced disease who are borderline candidates for anterior resection undergo 4500 cGy in 25 fractions in an attempt to permit them to have a sphincter-sparing procedure. Those patients with favorable lesions that are mobile, 3 cm or less in diameter, and exophytic, who would otherwise undergo an abdominoperineal resection, are treated conservatively with endocavitary radiation therapy or transrectal excision alone or combined with postoperative radiation therapy.[39-41] The remainder have surgery; postoperative radiation therapy and chemotherapy are added if disease extends through the muscularis or involves regional nodes.

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DISCUSSION

DR. RICHARD G. MARTIN (Houston, Texas): Dr. Ochsner, Dr. Jones, and Members, I want to thank the authors for the privilege of reviewing this manuscript. It is a very clear and excellent discussion on preoperative radiation. We have been doing preoperative radiation for quite some time at the M. D. Anderson Hospital. We differ a little from what Kirby does, but we come up with the same findings that he and his co-authors do. We still use the 4500 rads over a 25-day period. We have not had the experience with the lesser amounts over a shorter period. The economy of this is certainly understandable from the patient's point of view. And if the results are the same, I think it is advantageous. I did talk to Ty Rich, who does our radiation for this group regarding the lesser amount over a shorter period with higher fraction dose. He said he saw no reasons for increased complications, except that with the higher dose in fewer fractions you may get over a longer time more fibrosis.

The fields that we use are maybe a little larger than yours. We go to the promontory of the sacrum and the entire pelvic wall. In giving the radiation, they place the patient on a table prone. The table has a hole in it so that the abdomen can protrude through, and in this way we try to get the intestinal organs out of the pelvis. Our local recurrence rates are very similar to yours. As for our survival rates, we have had problems in trying to really accurately tell what they are. We know they are better, but it is hard to tell because of the downgrading. Now with the more advanced lesions, we are going to preoperative radiation plus chemotherapy simultaneously, and we have a group of about 21 cases. And of those 21 cases, we had eight in which there was no residual cancer found pathologically. I think that the preoperative radiation and possibly chemotherapy is far more advantageous than the postoperative radiation. I think this is an excellent paper, and I congratulate the authors. Thank you.

DR. COURTNEY M. TOWNSEND, JR. (Galveston, Texas): Dr. Ochsner, Dr. Jones, Members and Guests, the importance of this paper is emphasized by the juxtaposition of its presentation after Dr. Wanebo's paper. We all know the most difficult and most miserable cancer patient for whom we care is the patient with a pelvis full of recurrent rectal cancer. The group at Florida, using a treatment policy, not a randomized trial but nonetheless a treatment policy, since 1975, employing three different techniques of preoperative radiation, have almost eliminated local recurrence in the pelvis in patients with rectal cancer. This is a remarkable achievement, and one that is to be saluted as well as studied in the hope that it can be replicated.

A couple of questions arise from the consistent comment on the inability to compare either with historical controls or in a prospective trial because of downstaging. What were in fact the results of resected specimens examined pathologically in the patients who received preoperative radiation? Do you have any experience with the use of endorectal ultrasound in trying to determine the thickness of the wall involved, particularly based on the recommendation that a prospective trial be carried out? And, finally, how many of the patients were converted from a probable abdominal perineal resection to a sphincter-saving procedure? Would you also discuss the complications in those patients who had anastomosis, that is, instance of leak and perineal problems, if any, in the patients who had abdominal perineal? Thank you very much.

DR. J. SHELTON HORSLEY III (Richmond, Virginia): President Ochsner, Secretary Jones, I have enjoyed this presentation very much and appreciate the opportunity to review the manuscript. Certainly, Dr. Bland and his group have been in the leadership in this country and throughout the world in preoperative radiation for rectal cancer. It presents some real problems, as he has pointed out. First of all, we all are familiar with the problem of historical controls. There were 135 patients who underwent surgery alone between 1959 and 1976. In that control group, there were 53 Dukes C carcinomas of the rectum compared with the group of 132 that had preoperative radiation followed by resection, which only had 22 Dukes C carcinomas of the rectum. This would be fantastic downstaging for radiation, and I would like for him to comment on it.

Staging is the major problem. One hundred eighty-nine patients had preoperative irradiation, and only 132 were resected. Thirty per cent of the group had unnecessary irradiation. Now if you also add the Dukes A and Dukes B1 patients, which are excluded from preoperative radiation trials because it does not seem justified from the results we get, this figure is doubled to 59%. As Dr. Townsend has said, have you had experience with endorectal ultrasound? Certainly, the computed tomography scans and magnetic resonance imaging are helpful in staging, but none of these can give us the accurate staging that we get with surgical resection.

The second question I have is, how about the psychological effect on the patient who knows he or she has a rectal cancer and has to wait to undergo the preoperative procedure? Perhaps I should ask, how about the psychological effect on the surgeon?

Thirdly, this is crying for a clinical trial, no question about it. This is a good technique, has a lot of things in favor of it as opposed to postoperative irradiation, but we certainly do not know the answer. When we come to a clinical trial, because of the results with postoperative radiation showing that it will decrease local recurrence but not improve 5-year survival unless you add chemotherapy, it is going to be difficult to keep chemotherapy out of this. I enjoyed the presentation. It is an excellent manuscript; it was beautifully delivered. I thank you for the privilege of the floor.

DR. LOREN J. HUMPHREY (Columbia, Missouri): Dr. Ochsner, Dr. Jones, I thank you for letting me rise again. I will not reiterate some of the fine comments. I do think this will prompt a trial. And in a symposium I was on with Dr. Moertel, they had essentially written off preoperative radiation, notwithstanding the effects of downstaging.

My question is appropriate because Dr. Mendenhall is going to close this. And that is, one of the problems we have had in the use of surgery only or conservative surgery and radiation in our studies in trying to pick that subpopulation, at least early in the trials, has been that of delay. The delay from radiation therapy as emphasized by Borale was at least 300 days more in those who received radiation. In reviewing the world literature, Dr. Mendenhall, I really could not find anywhere in the previous studies, such as the Belgium and so forth, where they described delay in recurrence of, say, your surgery-only group *versus* those in surgery plus radiation whether preoperative or postoperative. I wonder, if you have that information, if you could share that with us. Thank you very much.

DR. WILLIAM MENDENHALL (Closing discussion): Dr. Ochsner, Dr. Jones, I appreciate the opportunity to close the discussion on this paper. I have been scribbling furiously, and I hope I am going to be able to recall most of the questions that were asked.

First of all, in response to Dr. Martin, 3000 rads in 10 treatments over 2 weeks we think is biologically equivalent to 4500 rads over 5 weeks. And the reason that we switched in 1984 to this treatment protocol was to decrease the treatment time by 3 weeks, from 5 weeks to 2 weeks, which makes it considerably more convenient and less expensive. The patients that have been presented and included in this series have been followed for a minimum of 5 years, and at least thus far, there is no increased incidence of late complications compared with patients in whom the radiation was fractionated over a longer period. With regard to field size, our fields are somewhat smaller, I think, than those that are used in many institutions. If you look at the literature, the best local control rates with preoperative radiation were obtained at the University of Oregon with 10 × 10-cm anterior-posterior fields. And so I do not think that small field size seems to be a problem. And I think that by using the smaller fields the treatment may be better tolerated and there will probably be a lower risk of a late complication.

In response to Dr. Townsend's question about downstaging, it is difficult to compare patients treated before operation with those who initially are treated with an operation and to know exactly how much downstaging there is. Eleven per cent of the patients had no residual tumor in the specimen, however, and the incidence of nodes has decreased by 50%. So I think that the incidence of downstaging is fairly significant.

We have only begun using endorectal ultrasound within the last year or two. And I really do not think that we have enough experience with that at the University of Florida to feel comfortable with exactly how useful that will be. From the literature, it appears that it is accurate in about 80% to 90% of cases, but I am sure that this is related to the experience of the ultrasonagrapher. As for the probability of converting patients who would need an abdominoperineal resection to an anterior resection, most of the patients in the series that were presented today underwent an abdominoperineal resection. And really we have only begun within the last 5 or 6 years to use preoperative radiation to try to convert patients to a sphincter-sparing operation. Most of those patients are not in this series, and so I really cannot comment on the number of patients in whom that was accomplished. As best we can tell in our experience to date now including patients who have been treated within the last 5 or 6 years, we have irradiated about 300 patients before operation. There is no obvious increased incidence in anastomotic leaks or perineal wound dehiscence in the group of patients treated with preoperative radiation therapy.

With regard to Dr. Horsley's comments, our definition of locally advanced was different for patients irradiated before operation than for those treated with surgery alone. The patients treated with preoperative radiation therapy were defined as being locally advanced based on clinical parameters, tethering, or annularity. Patients treated with surgery alone were pathologically staged. So these two patient populations are not really strictly comparable. And if anything, I think that the comparison is biased against the patients treated with preoperative radiation therapy, because there will be a fair number of lesions that are not tethered, that are not annular, that will be B2 or C lesions when they are operated. With regard to the number of patients excluded, 189 patients were treated with preoperative radiation therapy. Twenty-two per cent had lesions that were clinically unresectable to begin with, so those lesions were not included in this paper. Actually, 16 of 148 did not have a complete resection, and that winds up being about 10%. So about 10% of the lesions or patients when they were taken to surgery had liver metastases and were incompletely resected. We do advocate the use — the selective use — of preoperative radiation therapy. I do not think that everyone should get preoperative radiation. If clinically, and on the basis of endorectal ultrasound, the patient appears to have an early-stage lesion, then we think they should be operated initially.

As far as the psychological effect, if patients are advised that when they are receiving preoperative radiation the cancer is being treated — and the surgeons at the University of Florida and in the Gainesville area have worked with us for 15 or 16 years — at least as best I can tell, there has been no adverse psychological effect of delaying the surgery after preoperative radiation for either the patient or the surgeons. It might be best to talk to Dr. Copeland and Dr. Bland and see if they have been psychologically affected by that. To the best of my knowledge, that has not been the case.

I agree with the need for a clinical trial. I think that the momentum in this country is really moving in the direction of postoperative radiation and chemotherapy, and I regard this as somewhat unfortunate. I think that the treatment with postoperative radiation and chemotherapy is more difficult to get the patient through, it is more costly, there are more complications, and it may be no more effective than preoperative radiation, which can be given over a relatively short time period. I think I have answered all the questions. Thank you again for the opportunity to present our data to you and the opportunity to close the discussion. I appreciate it.

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NORTH CAROLINA: Vascular Surgeon sought by busy five-physician group in one of the state's most progressive cities. Affiliation with modern 275-bed hospital. Serve as Vascular Specialist for market area of 525,000 in this outstanding scenic location. Contact: **Bonnie Talton, AM Care Physician Search, Department J, P.O. Box 2816, Durham, NC 27715. 800-477-0600.**

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THERE IS MORE TO LIFE THAN MEDICINE. We'll give you all the time you need to discover this simple truth and still enjoy practicing quality medicine. As a member of our locum tenens group, you set your schedule; take large blocks of free time; catch up on postponed pleasures. . .or discover new ones. We expand your future practice opportunities, guarantee excellent income, provide malpractice insurance, make all the arrangements, and pay all the expenses. For details, contact your colleagues at **KRON Medical**, America's locum tenens group. Call toll free **1-800-MEDICAL** or write **KRON Medical Corporation, PO Box 13588, Research Triangle Park, NC 27709.**

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CHIEF OF SURGERY — The Sir Mortimer B. Davis - Jewish General Hospital, a 628 bed tertiary care teaching hospital of McGill University is inviting applications for the position of Chief of Surgery. The Department comprises the divisions of Cardio Vascular and Thoracic, Colorectal, General and Plastic Surgery. Potential candidates should be Royal College certified (or equivalent) and have significant academic and research experience in teaching hospitals. The successful candidate will be offered a university appointment commensurate with his/her qualifications. Interested candidates should send a copy of their curriculum vitae to: **Dr. P.L. Heilpern, Associate Executive Director, Professional Services, S.M.B.D. - Jewish General Hospital, 3755 Cote Ste-Catherine Road, Montreal, Quebec H3T 1E2.**

Assistant/Associate Professor — The University of Texas Medical Branch at Galveston, Department of Surgery is recruiting for a tenure eligible position as Chief of Vascular Surgery. Candidates must be Board Certified in General and Vascular Surgery and be eligible for Texas Licensure. Dedication to excellence in research, teaching and clinical service in an academic environment is essential. Send c.v. to: **James C. Thompson, M.D., John Woods Harris Professor and Chairman, Department of Surgery, Rt. E-27, The University of Texas Medical Branch, Galveston, TX 77550, Attn. Patti Mirakian.** UTMB is an Equal Opportunity/Affirmative Action Employer (M/F/V/H).

General and Vascular Surgeon seeking an associate. Must be BC/BE. Well established practice in a high growth area of suburban Seattle. This is a very unique opportunity. On the campus of a large, progressive medical center. 60,000 + ER visits/year. Excellent growth potential. Ideal environment for families, cultural pursuits and a wide variety of recreational activities. Send CV and your interests to: **Director of Physician Recruitment, 3330 S.W. 43rd St., Suite 154, Renton, Washington.**

SEATTLE - Group Health Cooperative of Puget Sound, a well-established 370,000-member prepaid group practice, is currently seeking a part-time General Surgeon. Practice surgery in a collegial atmosphere, with no primary care. To inquire, write to: **Medical Staff Personnel, 521 Wall Street, Seattle, WA 98121 or call 1-800-543-9323.**

GENERAL SURGEON/MILWAUKEE - Highly successful staff model HMO seeks a BC/BE general surgeon for an internal department of general and vascular surgery. Competitive salary and benefits. Please reply: **Kenneth Scher, M.D., F.A.C.S., Family Health Plan, 11524 W. Theo Trecker Way, Milwaukee, WI 53214, (414) 256-5691.**

GENERAL SURGEON - BC/BE General Surgeon with strong training in vascular surgery wanted to join a busy, well established group of seven. Physician will join large multispecialty group of 270, representing over 45 specialties. Main Clinic is adjacent to St. Luke's Hospitals, a 400 bed tertiary center and designated Trauma Center. Metropolitan community of 130,000 in the upper midwest offers an attractive life style for families. Excellent public and parochial schools. Two universities and a private liberal arts college offer many added amenities. Affiliation with U.N.D. Medical School and Surgery Residency program available. Please respond with full curriculum vitae to **Terrence Grimm, M.D., 737 Broadway, Fargo, ND 58123** or call **1-800-437-4010.**

San Francisco Bay Area — WANTED: Board Certified General or Subspecialty Surgeon to fill the position of Chief of Surgery at a 181-bed county hospital and large ambulatory care system located in the San Francisco Bay area. Responsibilities include: teaching the 27 residents of the hospital-based, U.C. Davis-affiliated Family Practice Residency Program; assisting in the development of the Family Practice faculty; general clinical and administrative duties; and the clinical and adminstrative supervision of the general and subspecialty surgeons. Salary and benefits negotiable. Please send C.V. to: **Steven Tremain, M.D., Director of Medical Staff Affairs, Merrithew Memorial Hospital, 2500 Alhambra Avenue, Martinez, CA 94553. Phone: 510-370-5110; FAX: 510-370-5142.** EOE.

GENERAL/VASCULAR SURGEON — BE/BC general surgeon with vascular experience to join a two surgeon group in Sunny Phoenix, Arizona. Send CV to: **North Valley Surgical Associates, P.C., 1728 West Glendale Avenue, Suite 401, Phoenix, Arizona 85021.**

GENERAL SURGERY — General surgeon needed in growing resort are in central Missouri ASAP. Recently expanded 99-bed hospital. Contact **(314) 348-6470** or send CT to **PO Box 797, Osage Beach, MO 65065.**

Director of Surgery - Saint Joseph Hospital, a 602-bed, not-for-profit teaching hospital located in the heart of Denver, Colorado, is searching for a Residency Program Director in the Department of Surgery. Currently 31 residents in entire program; 3 chief residents graduated annually. Candidates must be board certified in general surgery, have adequate clinical/surgical experience, show evidence of research interest with publication in peer reviewed journals, and must have been a faculty member in a surgical residency program. Saint Joseph Hospital is owned and operated by the Sisters of Charity of Leavenworth Health Services Corporation of Leavenworth, Kansas. As a teaching hospital, Saint Joseph holds a highly regarded reputation in residency training in internal medicine, surgery, obstetrics and gynecology, family practice and dentistry. It also participates in the training of emergency medicine residents and provides clinical rotations for third and fourth year medical students. Saint Joseph maintains the largest private surgery facility in the Rocky Mountain Region with over 20,000 surgical procedures performed each year. It also has five critical care units, delivers more than 5,000 babies each year, and has achieved national recognition for its cardiovascular surgery achievements. The Residency Program Director will be responsible for organizing and directing the training of surgical residents; for ensuring that all requirements of the Surgery Residency Review Committee are met or exceeded; for recruiting the most academically accomplished candidates for residency training; for representing Saint Joseph Hospital and the surgical training program through activities in regional and national scientific committees; for providing leadership in formulating both basic science and clinical research activities within the department; and for providing assistance with administrative duties for the Surgery Department and the Medical Staff. Saint Joseph Hospital is the leading hospital in the leading city in the Rocky Mountain West. Denver offers over 300 days of sunshine each year and easy access to a full range of world class outdoor and indoor recreational and cultural activities. Interested candidates should forward their curriculum vitae and bibliography to: **Peter Murr, M.D., Chairman, Department of Surgery Education Search Committee, Saint Joseph Hospital, 1835 Franklin Street, Denver, CO 80218,** an equal opportunity employer.

PHYSICIAN: CHIEF OF SURGERY. The University of South Florida, Department of Surgery, and the Department of Veteran's Affairs, located in Tampa Bay area, are seeking applicants at the level of Associate Professor or Professor to be Chief, surgical service at the Bay Pines VA Medical Center. The hospital is a modern 1,100 bed facility, located in the Gulf Coast area and offering various levels of general medical and surgical care. Board certification in general surgery and excellent clinical and teaching credentials are essential. Research and administrative experience is highly desirable. Interested candidates may forward inquiries and an updated Curriculum Vitae to: **Chairperson, Search Committee (111), VA Medical Center, Bay Pines, FL. 33504.** EOE.

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TIMENTIN® **sterile ticarcillin disodium and clavulanate potassium** for Intravenous Administration

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

INDICATIONS AND USAGE: *Timentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:
Septicemia: including bacteremia, caused by β-lactamase-producing strains of *Klebsiella* spp.*, *E. coli*,* *Staphylococcus aureus** and *Pseudomonas aeruginosa** (and other *Pseudomonas* species*). Lower Respiratory Infections: caused by β-lactamase-producing strains of *Staphylococcus aureus, Hemophilus influenzae** and *Klebsiella* spp.* Bone and Joint Infections: caused by β-lactamase-producing strains of *Staphylococcus aureus*. Skin and Skin Structure Infections: caused by β-lactamase-producing strains of *Staphylococcus aureus, Klebsiella* spp.*, and *E. coli*.* Urinary Tract Infections (complicated and uncomplicated): caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa** (and other *Pseudomonas* spp.*), *Citrobacter* spp.*, *Enterobacter cloacae*,* *Serratia marcescens** and *Staphylococcus aureus*.* Gynecologic Infections: endometritis caused by β-lactamase-producing strains of *B. melaninogenicus*,* *Enterobacter* spp. (including *E. cloacae**), *Escherichia coli*, *Klebsiella pneumoniae*,* *Staphylococcus aureus* and *Staphylococcus epidermidis*. Intra-abdominal Infections: peritonitis caused by β-lactamase-producing strains of *Escherichia coli*, *Klebsiella pneumoniae* and *Bacteroides fragilis** group.
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While *Timentin* is indicated only for the conditions listed above, infections caused by ticarcillin-susceptible organisms are also amenable to *Timentin* treatment due to its ticarcillin content. Therefore, mixed infections caused by ticarcillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Timentin* should not require the addition of another antibiotic.

ADVERSE REACTIONS: As with other penicillins, the following adverse reactions may occur: *Hypersensitivity reactions:* skin rash, pruritus, urticaria, arthralgia, myalgia, drug fever, chills, chest discomfort and anaphylactic reactions. *Central nervous system:* headache, giddiness, neuromuscular hyperirritability or convulsive seizures. *Gastrointestinal disturbances:* disturbances of taste and smell, stomatitis, flatulence, nausea, vomiting and diarrhea, epigastric pain and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). *Hemic and lymphatic systems:* thrombocytopenia, leukopenia, neutropenia, eosinophilia and reduction of hemoglobin or hematocrit. Prolongation of prothrombin time and bleeding time. *Abnormalities of hepatic and renal function tests:* elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum LDH, serum bilirubin. Rarely, transient hepatitis and cholestatic jaundice—as with some other penicillins and some cephalosporins. Elevation of serum creatinine and/or BUN, hypernatremia. Reduction in serum potassium and uric acid. *Local reactions:* pain, burning, swelling and induration at the injection site and thrombophlebitis with intravenous administration. *Overdosage:* As with other penicillins, *Timentin* in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures. Ticarcillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by hemodialysis.

CONTRAINDICATIONS: *Timentin* is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *TIMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, *TIMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Timentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of ''antibiotic-associated colitis.''

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibiotic drug effective against *C. difficile*.

PRECAUTIONS: While *Timentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, organ system functions should be assessed periodically during therapy.

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics. These reactions have been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. If bleeding manifestations appear, *Timentin* treatment should be discontinued and appropriate therapy instituted.

Timentin has only rarely been reported to cause hypokalemia. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

Pregnancy (Category B): Reproduction studies have been performed in rats given doses up to 1050 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to *Timentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

DOSAGE AND ADMINISTRATION: *Timentin* should be administered by intravenous infusion (30 min.). Usual recommended dose for systemic and urinary tract infections for average (60 kg) adults is 3.1 grams *Timentin* (3.1 gram vial containing 3 grams ticarcillin and 100 mg clavulanic acid) given every four to six hours. For gynecologic infections *Timentin* should be administered as follows: Moderate infections 200 mg/kg/day in divided doses every six hours and for severe infections 300 mg/kg/day, based on ticarcillin content, in divided doses every four hours. For patients weighing less than 60 kg, the recommended dosage is 200-300 mg/kg/day, based on ticarcillin content, given in divided doses every four to six hours. In urinary tract infections, a dosage of 3.2 grams *Timentin* (3.2 gram vial containing 3 grams ticarcillin and 200 mg clavulanic acid) given every eight hours is adequate. Please see complete prescribing information for details on dosages for other patients, including those with renal insufficiency, and directions for use.

HOW SUPPLIED: 3.1 gram Standard Vial; 3.1 gram Piggyback Bottle; 31 gram Pharmacy Bulk Package; 3.1 gram ADD-Vantage® Antibiotic Vial.

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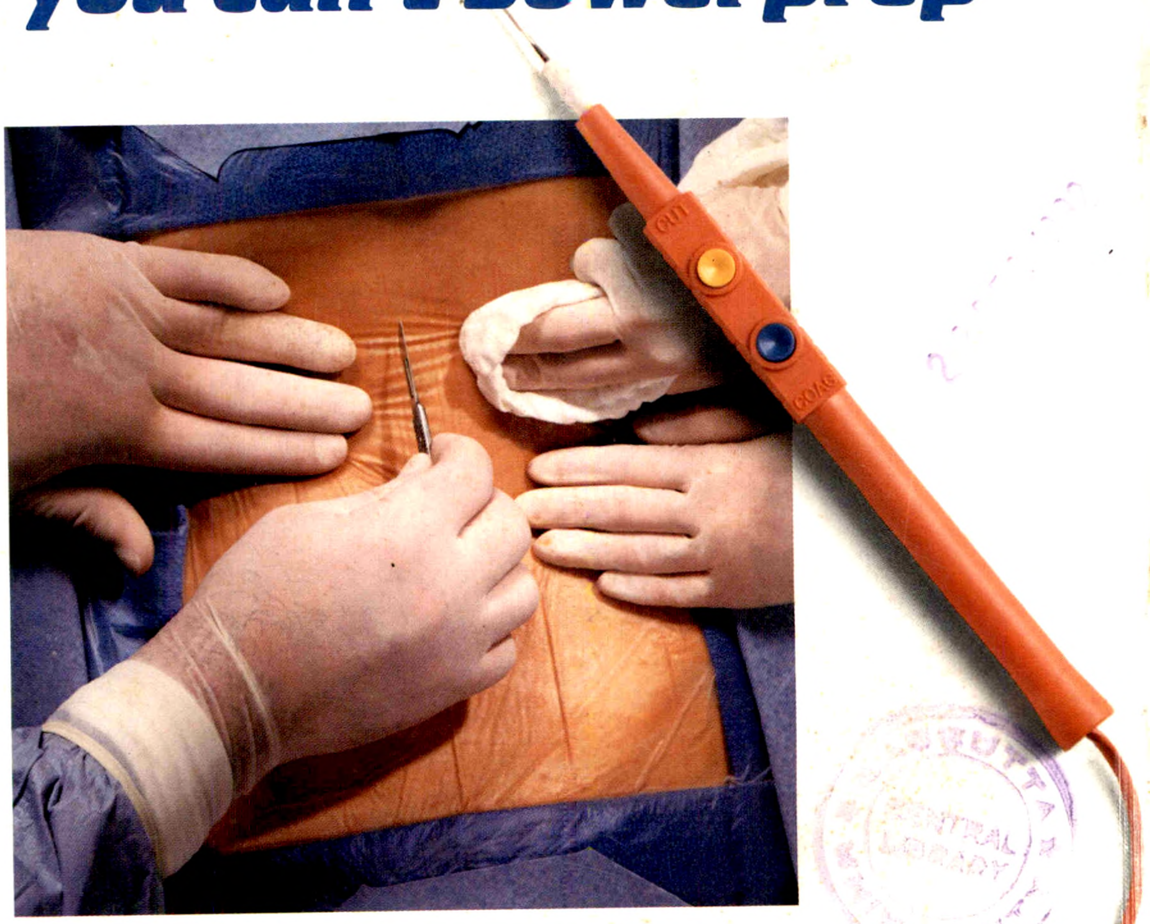
Pharmaceuticals

When you can't bowel prep—



Ninety percent of the patients with intra-abdominal infections* receiving Timentin® were clinically cured or improved compared to 83% of the patients receiving clinda/aminoglycoside/± amp.[†] Timentin® provided superior eradication of β-lactamase-positive pathogens ($P=0.05$[‡]), including *E. coli* ($P=0.03$[‡]).[1]

TIMENTIN®

ticarcillin disodium/
clavulanate potassium

3.1 g
q6h§

Made for mixed infections

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*Infections (N=256) caused by one or more β-lactamase-producing pathogens.

[†] Eleven patients received clinda/aminoglycoside/amp.

[‡] Chi-square method.

[§] Please see brief summary of prescribing information on adjacent page for dosage and administration.

[1] Data on file, SmithKline Beecham Pharmaceuticals.

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